University of Alberta

Development of novel three-component [4+2] cycloaddition/allylboration reactions and their applications in natural product synthesis

by

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of the

requirements for the degree of Doctor of Philosophy

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Abstract

The three-component normal electron demand Diels-Alder cycloaddition/allylboration reaction constitutes a powerful way to access highly functionalized α-hydroxyalkyl-substituted six-membered carbo- or heterocycles. The intrinsic low reactivity of 1-boronobutadienes in the cycloaddition step, however, significantly limits the application of this three-component reaction. Chapter 2 of this thesis describes the preparation and the behavior of two electron-rich ether-substituted 1-boronobutadienes in the three-component reaction involving an electron- poor dienophile and an aldehyde. Whereas 1-borono-4-methoxy-1,3-butadiene pinacolate failed to undergo the second allylboration step of the process, 1-borono-3-triethylsilyloxy-1,3-butadiene pinacolate did give the desired final products from the three-component reaction. The use of 1-borono-3-triethylsilyloxy-1,3-butadiene pinacolate in the three-component reaction provides a new stereoselective approach to oxygenated cyclohexene derivatives with a stereodefined α-hydroxyalkyl substituent.

The development of the first catalytic enantioselective hetero-Diels-Alder cycloaddition/allylboration process catalyzed by Jacobsen's Cr(III) catalyst is presented in Chapter 3. From the key substrate 3-boronoacrolein pinacolate, this one-pot, three-component reaction provides α-hydroxyalkyl dihydropyrans with very high enantio- and diastereoselectivity. 3-Boronoacrolein pinacolate demonstrated exceptional reactivity in the inverse electron demand cycloaddition step, and this reactivity can be tentatively

explained by a [5+2] transition state reminiscent to that of Singleton's vinylborane cycloadditions.

The chiral α-hydroxyalkyl dihydropyrans made by the three-component reaction can be used as starting materials for the construction of a number of biologically interesting natural products. Chapter 4 describes the total synthesis of (5*R*,6*S*)-6-acetoxy-hexadecanolide, the major component of the oviposition attractant pheromone of *Culex* mosquito (the primary vector of West Nile Virus), and its C6 epimer using the three-component methodology.

Thiomarinols are very promising leads for antimicrobial drug discovery. The first total synthesis of a member of the potent thiomarinol class of antibiotics is detailed in Chapter 5. The key step in the synthesis is the efficient catalytic enantio-, regio-, *E*/*Z*-, and diastereoselective inverse electron demand hetero-Diels-Alder cycloadition/allylboration sequence. A number of simplified analogues of thiomarinols were also prepared based on the newly developed three-component route. Gratifyingly, two simplified ester analogues demonstrate improved activity against *Staphylococcus aureus*.

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List of Abbreviations

Ac	Acetyl
AcOH	Acetic acid
Ac_2O	Acetic anhydride
Anal.	Elemental analysis
APT	Attached proton test
Ar	Aryl
Bn	Benzyl
BOM	benzyloxymethyl
brs	Broad singlet
Bu	butyl
s-Bu	*sec*-Butyl
Calcd	Calculated
CDI	1,1'-Carbonyldiimidazole
Cy	Cyclohexyl
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dddd	Doublet of doublets of doublets of doublets
de	Diastereomeric excess
DIBAL-H	Di-*i*-butylaluminum hydride
DIAD	Diisopropyl azodicarboxylate
DIC	Diisopropylcarbodiimide
DIPEA	Diisopropylethylamine
DMAP	4-(*N*,*N*)-Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
ee	Enantiomeric excess
EI	Electron Impact
equiv.	Equivalents
ES	Electrospray

Et	Ethyl
FTIR	Fourier-Transform Infrared
h	hour/hours
HDA	Hetero-Diels-Alder
HMPA	Hexamethylphosphoramide
HOBT	1-Hydroxybenzotriazole
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IDCP	Iodo(bis)collidine perchlorate
Ipc	Isopinocampheyl
IR	Infrared
KHMDS	Potassium hexamethyldisilazide
LA	Generic Lewis acid
m	Multiplet
*m*CPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligrams
min	Minute/minutes
mL	Milliliters
mmol	Millimoles
MOM	methoxymethyl
m.p.	Melting point
MS	Mass Spectrometry
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	Trifluoromethanesulfonate
PDC	Pyridinium dichromate
PG	Protective group

Ph	Phenyl
ppm	parts per million
Pr	Propyl
PS	Polystyrene
PyBroP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	Quartet
R	Generic alkyl group
rt	Room temperature
s	Singlet
Sharpless AD	Sharpless asymmetric dihydroxylation
Sharpless AE	Sharpless asymmetric epoxidation
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*t*-Butyldimethylsilyl
TBDPS	*t*-Butyldiphenylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TFA	Trifluoroacetic acid
TLC	Thin Layer Chromatography
Ts	Toluenesulfonyl

Chapter1

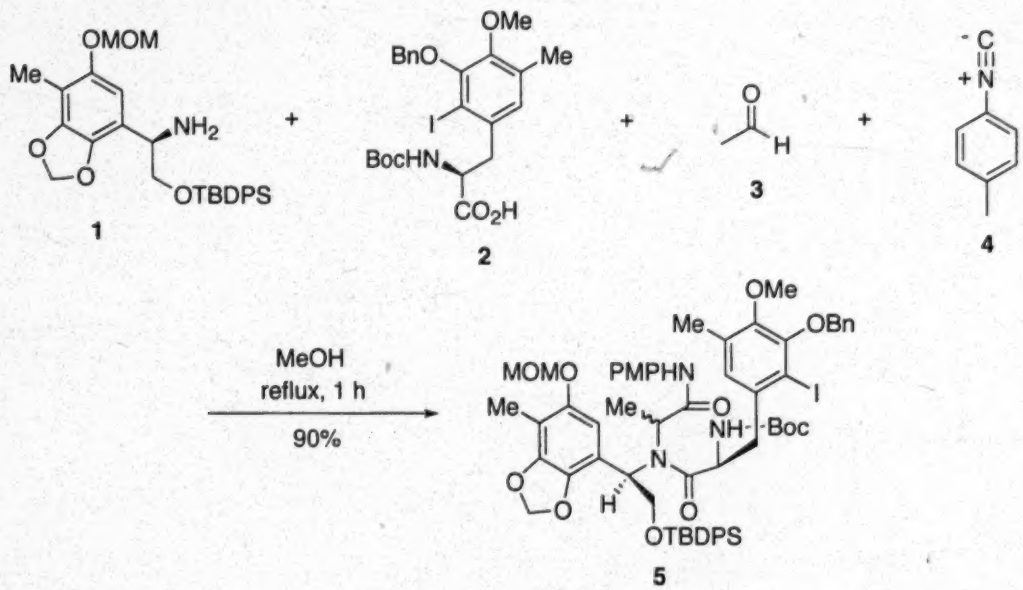
Introduction: Three-Component Diels-Alder Cycloaddition/Allylboration Reaction in Organic Synthesis

1.1 Introduction

Since the milestone synthesis of urea by Wöhler in 1828,[1] organic synthesis has developed into one of the most challenging and exciting areas of chemistry. The goal of organic synthesis is to develop methods and strategies allowing the synthesis of desired natural and unnatural organic compounds from simple starting materials. Among different areas in organic synthesis, the development of new synthetic methods is one of the most important driving-force for the advance of the entire discipline. Significant progress has been achieved during the past decades, and many highly chemo- diastereo- and enantioselective single bond forming reactions have been invented. These discoveries have dramatically changed the strategies for constructing complex organic molecules. However, with the isolation of more and more complex biologically active natural products and the development of combinatorial chemistry, there is an urgent need for more efficient methodologies to generate molecular complexity. Developing new multicomponent reactions (MCRs) that allow multi-bond formation in a single operation is one of the most attractive approaches to meet the demand.[2]

Currently, there are several different definitions for a multicomponent reaction. In the present context, we define multicomponent reactions, regardless of their mechanistic nature, as processes in which three or more reactants are combined either simultaneously

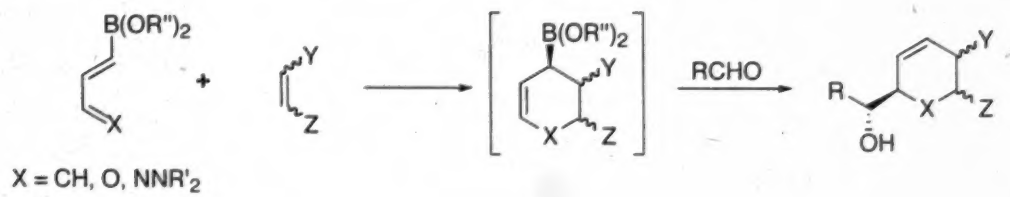
("pure" MCRs), or through a sequential addition procedure that does not involve any change of solvent. With respect to their chemical efficiency, convergence and the ability to generate molecular diversity and complexity, multicomponent reactions occupy an outstanding position among all other reactions and are highly appealing in the context of both target- and diversity-oriented synthesis. There are a number of brilliant applications of MCRs in organic synthesis, with one of the most recent examples being that of Fukuyama and co-workers. Here, a novel Ugi four-component reaction was used to construct the key intermediate of *Ecteinascidin 743,* a natural substance displaying high *in vitro* cytotoxicity (Equation 1-1).[3]



Equation 1-1

1.2 Three-component Diels-Alder cycloaddition/allylboration reaction

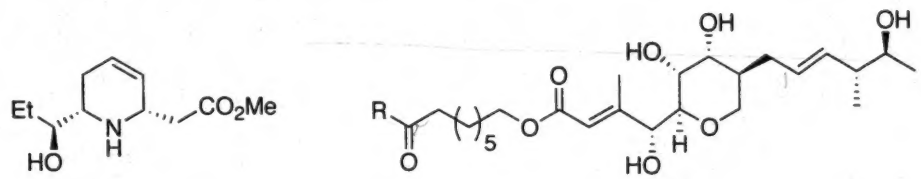
Many of the established MCRs were found by serendipity rather than by rational planning. However, with the growing knowledge of reaction mechanisms, a number of powerful MCRs have been developed through rational design. Among these reactions, the three-component Diels-Alder cycloaddition/allylboration reaction has been one of the most impressive classes of MCRs developed by rational design to date (Scheme 1.1). This reaction was first used by Vaultier and co-workers to synthesize α-hydroxyalkyl cyclohexenes in 1987.[4] Inspired by the pioneering work of Vaultier, Lallemand and co-workers have spent great effort to refine this methodology[5] and developed the "one-pot" variant.[5d] More recently, this methodology has been extended to access α-hydroxyalkyl piperidines by Hall[6] and α-hydroxyalkyl dihydropyrans independently by Hall and Carboni.[7]



Scheme 1.1

In these reaction sequences, the simple 1-borono-butadienes and hetero-dienes first undergo regio-, diastereo- and sometimes enantioselective Diels-Alder cycloaddition reactions with a variety of dienophiles providing six-membered cyclic allylboronates. Without isolating the cyclic allylboronate intermediate, further reaction with aldehydes generates the final highly functionalized hydroxyalkyl-substituted six-membered

unsaturated carbo or heterocycles. It should be noted that the process usually leads to excellent diastereoselectivity. This sequence combines both the powerful Diels-Alder and allylboration reactions in order to build up molecular complexity in a single operation (i.e. a "one-pot" reaction). This makes the approach a very attractive strategy in the synthesis of natural products and natural product-like libraries that contain hydroxyalkyl-substituted six-membered carbocyclic or heterocyclic units, such as those found in (-)-methyl palustramate[8] and thiomarinols[9] (Figure 1-1).



(-)-methyl palustramate thiomarinols

Figure 1-1. Selected examples of natural products containing α-hydroxyalkyl six-membered heterocycles

In order to better understand this process, the two mechanistic steps involved will be discussed separately in the following two sections.

1.2.1 Diels-Alder cycloaddition reaction

Since its discovery by Otto Diels and Kurt Alder in 1926,[10] the Diels-Alder reaction and its many variants have arguably been the most useful and powerful methods available to the synthetic chemist. These reactions are normally easy to perform and often proceed in a high regio- and diastereoselective manner, and thus, are extensively utilized in organic synthesis.[11]

In order to explain the reactivity and selectivity observed in Diels-Alder reactions, frontier molecular orbital (FMO) theory,[12] developed by Fukui, has been successfully applied.[13] Based on the dominant interactions of the FMOs of the diene and dienophile in the transition state, Diels-Alder reactions have been classified into three general types, which are termed the normal, neutral and inverse electron demand Diels-Alder reaction. In the normal electron demand Diels-Alder reaction involving electron-rich dienes and electron-deficient dienophiles, the dominating orbital interaction is the $HOMO_{diene}$-$LUMO_{dienophile}$ (Figure 1-2). The inverse electron demand Diels-Alder reaction that predominantly takes place between electron-deficient dienes and electron-rich dienophile is mainly controlled by the $LUMO_{diene}$-and $HOMO_{dienophile}$ interaction. In the neutral electron demand reaction, neither frontier orbital interaction dominates.

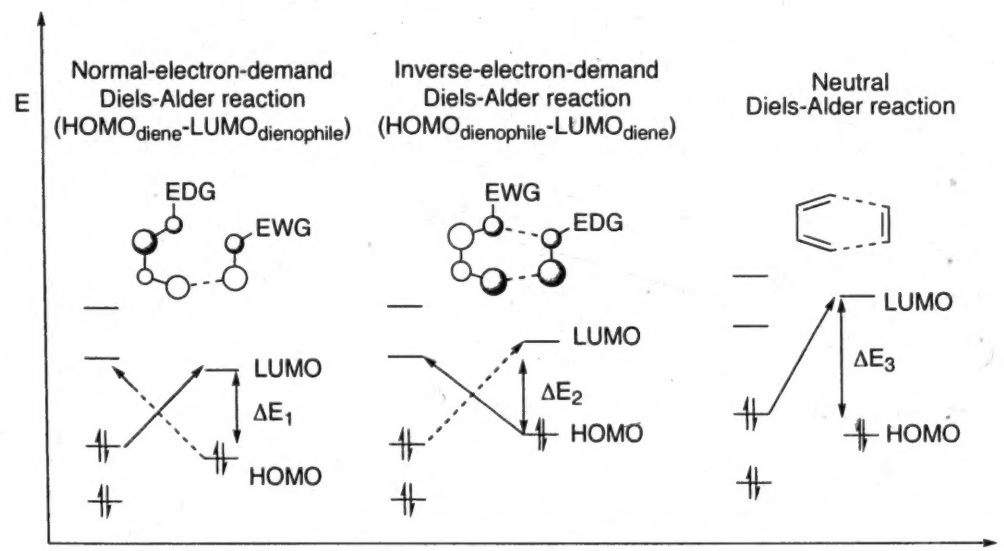


Figure 1-2. Classes of Diels-Alder reactions according to FMO interactions

The reactivity of a Diels-Alder reaction is determined by the lowest HOMO-LUMO energy difference that can be achieved by the reaction partners. All factors that lower the HOMO-LUMO energy gap increase the reaction rate because a smaller energy difference between interacting FMOs leads to a greater stabilization of the transition state. Reactivity is predicted on the basis of the effects that substituents impose on the MOs of the diene and dienophile. Electron-withdrawing substituents lower the energy of both HOMO and LUMO molecular orbitals, whereas electron-donating groups raise their energies. As reactivity increases when the energy difference between interacting FMOs decreases, in the normal electron demand Diels-Alder reaction, an electron-donating substituent on the diene will accelerate the reaction, whereas an electron withdrawing substituent on the diene will retard it. Conversely, an electron-withdrawing substituent in the dienophile will accelerate the reaction while an electron-donating substituent on the dienophile will retard it. In the case of inverse electron demand Diels-Alder reactions, the electronic effect of the substituents influences reactivity in an opposite way. The energy difference of interacting FMOs in normal and inverse electron demand Diels-Alder reaction is usually far smaller than that of neutral electron demand Diels-Alder reactions. As such, the vast majority of the reported Diels-Alder reactions are normal and inverse electron demand Diels-Alder reactions, which often proceed under very mild conditions. In sharp contrast, the requirement for forcing conditions in the neural electron demand Diels-Alder reactions severely limited their use in organic synthesis until the relatively recent discovery of transition metal-catalyzed cycloaddition.[14]

1.2.2 Lewis acid catalyzed Diels-Alder reaction

In 1960, Yates and co-workers were the first to report that the rate of Diels-Alder reactions could be accelerated in the presence of a Lewis acid.[15] Since then, Lewis acid catalyzed Diels-Alder reactions have received great attention because the catalysts allow the reactions to be carried out under milder conditions. This also opens up the use of dienes or dienophiles that were previously thought to be unreactive as valuable reaction partners. Furthermore, Lewis acid catalyzed Diels-Alder cycloadditions are usually more regio- and stereoselective than their thermal counterpart.

FMO theory has also been successfully used to explain the role of the Lewis acid catalyst in the Diels-Alder reaction. By forming a complex with the basic center of the dienophile in the normal electron demand Diels-Alder reaction, the catalyst decreases the electron density in the π- system. This interaction thus lowers the energy of the LUMO of the dienophile. As a consequence, the energy difference between $HOMO_{diene}$ and $LUMO_{dienophile}$ decreases (Figure 1-3). In the inverse electron demand Diels-Alder reaction, the coordination of the Lewis acid to a heteroatom in the diene lower the LUMO energy of the diene, resulting in a decrease of the $LUMO_{diene}$-$HOMO_{dienophile}$ gap. Thus, better orbital overlap is obtained.

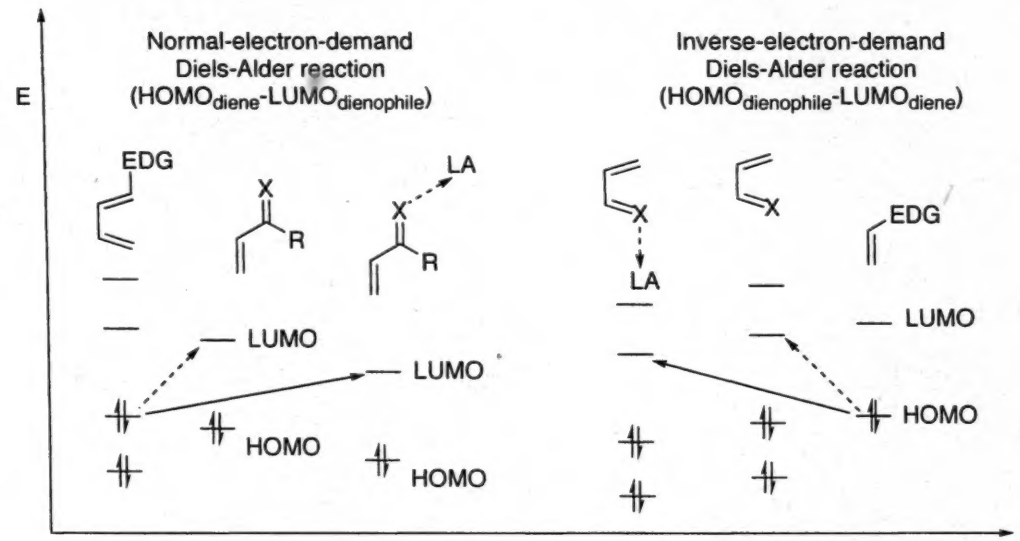
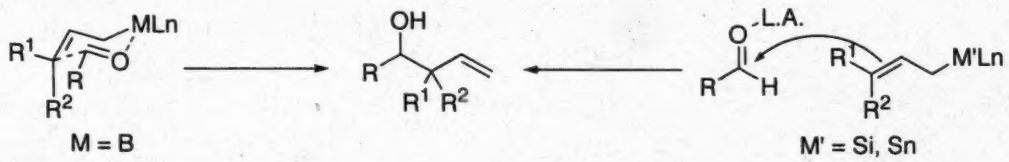


Figure 1-3. The role of the Lewis acid in Diels-Alder reactions

Over the last two decades, the focus of research on Lewis acid catalyzed Diels-Alder reactions has progressed to the development of catalytic asymmetric variants, in order to obtain optically pure products.[16] To achieve a catalytic asymmetric Diels-Alder reaction, coordination of a chiral Lewis acid to the basic center of one reaction partner is essential. This coordination event activates the substrate and provides a chiral environment that forces the approach of the second reaction partner from the less steric hindered face, introducing enantioselectivity in the reaction. With the recent development of asymmetric catalysis, highly functionalized six-member carbon or heterocycles can be accessed in enantiopure form through these reactions.

1.2.3 Allylboration

Carbonyl allylation is one of the most efficient strategies for the generation of homoallylic alcohols, which are very useful precursors for the construction of polyacetate and polypropionate natural products.[17] Denmark has classified the different allylmetal reagents into two groups according to their different reaction mechanism, whether they proceed through a closed or open transition state (Figure 1-4).[18]



Type I	Type II
-Closed, six-membered chairlike T.S.	-Open T.S.
-Does not require external Lewis acid activation	-Requires external Lewis acid activation
-Usually highly stereoselective, predictable	-Usually not highly stereoselective

Figure 1-4. Type I and Type II allylation reagents

Allylboranes and allylboronates belong to the Type I class of allyl transfer reagents, as they undergo addition reactions with aldehydes via a closed Zimmerman-Traxler transition state. In the allylboration transition state, boron acts as an internal Lewis acid, activating the aldehyde by coordinating with the oxygen lone pair of the aldehyde. As a result of the self-activation, allylboryl species are much more reactive than allylsilanes and stannanes, and can add to aldehydes without the presence of an external Lewis acid at a lower temperature.

Due to the compact, organized nature of the cyclic Zimmerman-Traxler transition state, allylation with allylboryl reagents generally shows higher diastereoselectivities than reactions with the corresponding Type II reagents, such as allylsilanes and stannanes. Furthermore, the stereochemistry of the product of allylboration is readily and reliably predicted by cyclic six-membered chair-like models. Generally, *Z*-reagents afford *syn*-configured products and *E*-reagents afford *anti*-configured products. In addition, the chirality of the allylboryl reagent can be transferred to the allylation products in many cases.

According to a study by Brown and co-workers, the reactivity of allylboryl reagents towards carbonyl compounds was found to be closely related to the electrophilicity of the boron atoms.[19] This result can be explained by high level calculations, which have shown that the boron-oxygen coordination is the determinant factor in the reaction rate, and most of the C-C bond formation occurs after the transition state.[20] In light of these studies, Hall and co-workers discovered that the allylboration reaction could be accelerated through the addition of an external Lewis Acid with no apparent loss of stereospecifity.[21] They demonstrated that a catalytic amount of Lewis acid was capable of providing dramatic rate enhancements in the allylboration reactions compared to the uncatalyzed process. Under the catalytic conditions, reactions that previously took 16-18 h at 110 °C are now complete after stirring overnight at ambient temperature. On the basis of the potential beneficial effect of a lower reaction temperature, a remarkably general and practical enantioselective allylation methodology was developed. This powerful method is based on the $Sc(OTf)_3$ catalyzed reaction of

stable Hoffman's camphor-derived boronates.[22] Subsequent mechanistic studies proved that the rate enhancement of the Lewis acid catalyzed addition of allylboronates to aldehydes stemmed from electrophilic boron activation by coordination of the metal ion to one of the boronate oxygens in a closed transition state.[23] Shortly thereafter, Miyaura and co-workers independently described the use of Lewis acids to catalyze the addition of allyl and crotylboronates to aldehydes.[24] This group also reported an enantioselective addition using a catalytic amount of a chiral Lewis acid. However, only moderate enantiomeric excess was observed.

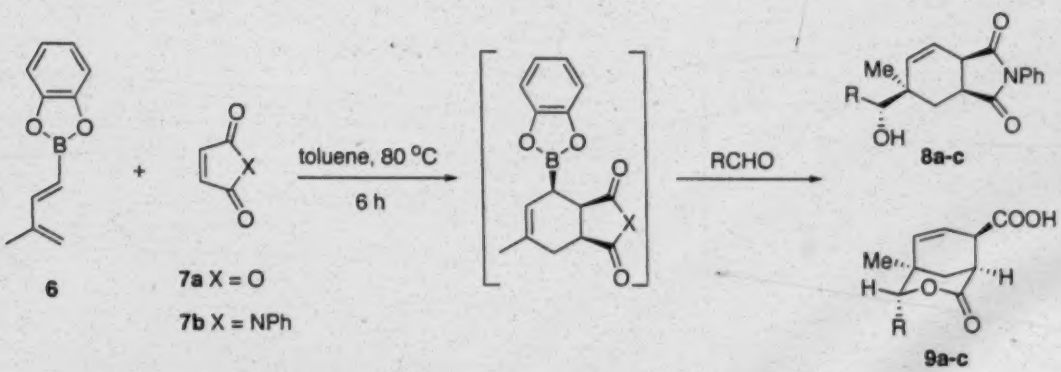
1.3 Recent advances in the development and application of the three-component Diels-Alder cycloaddition/allylboration reaction

1.3.1 Three-component Diels-Alder cycloaddition/allylboration reaction.

Although the Diels-Alder reaction between 1,3-dienyl boronates and maleic anhydride has been known for more than thirty years,[25] it was first demonstrated by Vaultier and co-workers that the six-membered cyclic allyl boronate adducts made from the Diels-Alder reaction could be trapped in "one-pot" with a variety of aldehydes to afford the α-hydroxyalkyl cyclohexene derivatives with high diastereoselectivity.[4] For example, the boronate **6** underwent a completely *endo*-selective cycloaddition with maleic anhydride and *N*-phenyl maleimide to give the expected adducts in a quantitative yield. After completion of the cycloaddition step, aldehydes were added to the reaction mixture and the final allylboration products were obtained in good yields and high

diastereoselectivity (Table 1-1). The stereochemistry of the final α-hydroxyalkyl cyclohexene derivatives was elucidated by NMR spectroscopy and X-ray crystallography. The stereochemical outcome of this reaction is in line with the stereochemistry obtained in additions of a *Z*-crotylboronate to an aldehyde.

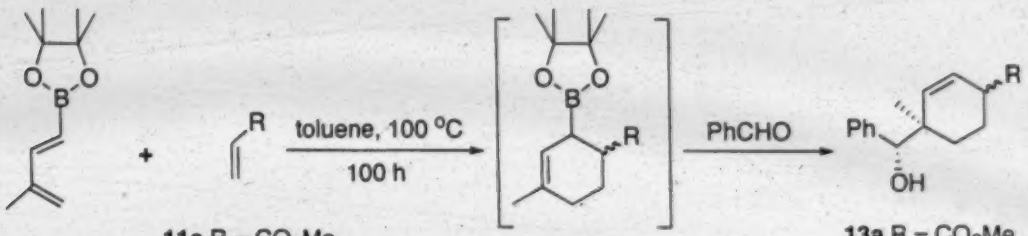
Table 1-1. The three-component Diels-Alder cycloaddition/allylboration reaction of diene 6



Entry	Dienophile (X)	Aldehyde (R)	Product	Yield (%)
1	NPh	Ph	**8a**	69
2	NPh	*i*-Pr	**8b**	67
3	NPh	Et	**8c**	66
4	O	Ph	**9a**	80
5	O	*i*-Pr	**9b**	75
6	O	Et	**9c**	70

The use of mono-activated dienophiles such as methyl acrylate in the three-component reaction was also studied. Unlike maleic anhydride and maleimides, mono-activated dienophiles are poor reaction partners in the Diels-Alder reaction with unactivated 1-boronobutadienes. The reaction conditions are rather harsh, often requiring

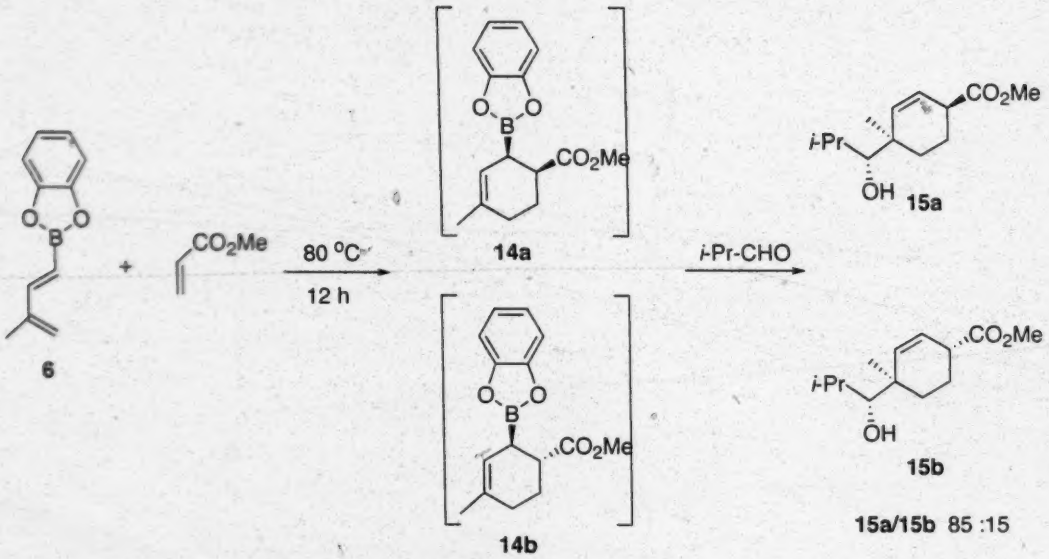
high temperatures and long reaction times. In addition, the diastereoselectivity of the reaction is usually not favourable.[20] For example, the Diels-Alder reaction of boronate **10** with methyl acrylate or acrylonitrile requires 100 hours at 100 °C to go to completion, and the resulting adducts **12a** and **12b** were obtained as a mixture of *endo* and *exo* diastereomers. The adducts **12a** and **12b** were further reacted with benzaldehyde to afford the respective homoallylic alcohol products as a mixture of diastereomers (Scheme 1.2).



10 + **11a** R = CO_2Me, **11b** R = CN → **12a** R = CO_2Me, *endo/exo* 1 : 1.8; **12b** R = CN, *endo/exo* 1 : 1.6 → **13a** R = CO_2Me, **13b** R = CN

Scheme 1.2

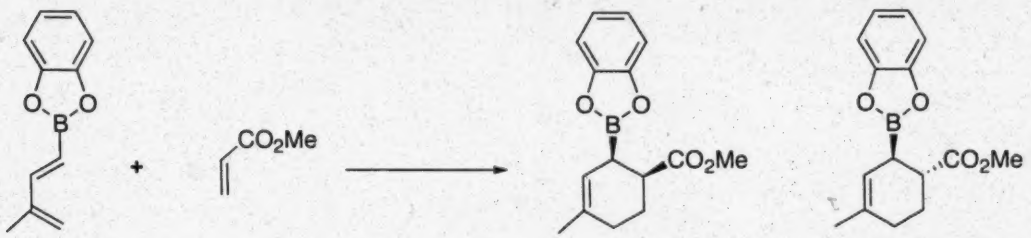
One way to improve efficiency and selectivity of the Diels-Alder reaction is to conduct the reaction without solvent. Thus, the reaction of boronate **6** with methyl acrylate under neat conditions afforded the *endo*-allylboronate **14a** and *exo*-allylboronate **14b** in a ratio of 85:15. Unsurprisingly, the corresponding α-hydroxyalkyl cyclohexene derivatives **15a** and **15b** were also obtained as 85:15 mixtures after the allylation reaction of **14a** and **14b** with isobutyraldehyde (Scheme 1.3).[5a] This result confirms the idea that the diastereoselectivity of the allylboration reaction is fully controlled by the usual six-membered chair-like transition state.



Scheme 1.3

For less active dienophiles, another successful approach is to activate dienophile by Lewis acid catalyst. Lallemand and co-workers examined a number of Lewis acids using boronate **6** and methyl acrylate as reaction partners.[5b] As summarized in Table 1-2, $EtAlCl_2$ afforded the best results amongst the Lewis acids tested in the reaction and stoichiometric amounts of Lewis acid were required to obtain high yields. The reaction time was reduced and the diastereoselectivities of the products were improved compared with the same reaction without a Lewis acid catalyst. With Et_2AlCl, the allylation reaction could be performed efficiently as previously described. In the case of $EtAlCl_2$, one equivalent of Et_3N had to be added before the addition of the aldehyde in order to obtain the desired product. This seminal work with Lewis acids opens the door toward developing catalytic asymmetric version of these powerful reactions.

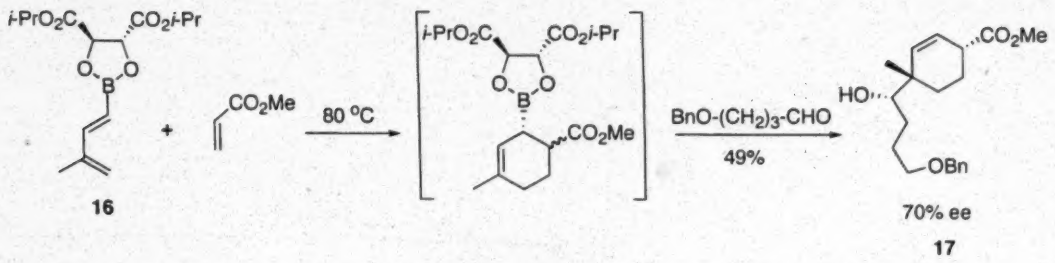
Table 1-2. Lewis acid catalyzed Diels-Alder reaction of diene 6 with methyl acrylate



6 14a 14b

Lewis Acid	Solvent	Temperature (°C)	Time (h)	**14a/14b**
None	C_6H_6	80	24	80/20
Et_2AlCl	C_6H_6	80	4.5	85/15
$EtAlCl_2$	CH_2Cl_2	20	6	>95/5
$EtAlCl_2$	CH_2Cl_2	0	50	>95/5
$AlCl_3$	CH_2Cl_2	0	diene polymerizes	
$TiCl_4$	CH_2Cl_2	0	diene polymerizes	
$BF_3 \bullet Et_2O$	CH_2Cl_2	0	no reaction after 6 h	
$BF_3 \bullet Et_2O$	CH_2Cl_2	0	diene decomposes	

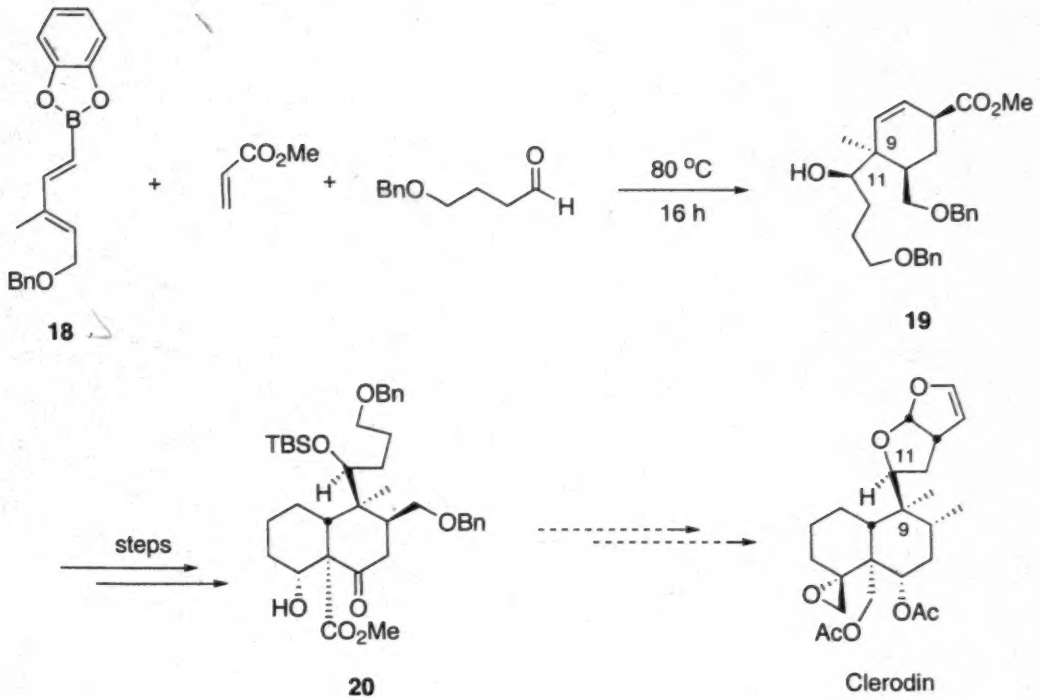
Because the three-component Diels-Alder cycloaddition/allylboration reactions show great potential in organic synthesis, it has become attractive to develop an enantioselective version of this process. Thus, chiral boronate **16** was synthesized and tested in the three-component reaction using methyl acrylate as dienophile and 4-benzyloxy-butyraldehyde. A moderate enantiomeric excess of 70% was obtained for the major diastereomer **17** (Scheme 1.4).[5c]



Scheme 1.4

1.3.2 Application in natural product synthesis

In their synthetic studies toward Clerodin, a structurally complex diterpene exhibiting remarkable antifeedant activity against insects, Lallemand and co-workers employed a three-component Diels-Alder cycloaddition/allylboration strategy to construct the advanced intermediate **19** in two steps from the functionalized dienylboronate **18** (Scheme 1.5).[5d, 5e] This synthetic sequence also gave complete control over the relative configurations at C9 and C11 of the natural product. The intermediate **19** was transformed to compound **20**, which possesses most of the functionality of the natural product. Notably, this sequence represented the first example in which all three of the components of the reaction were combined simultaneously instead of the usual sequential addition procedure. This alteration further simplified the operation of this powerful three-component reaction and usually provides better yields.



Scheme 1.5

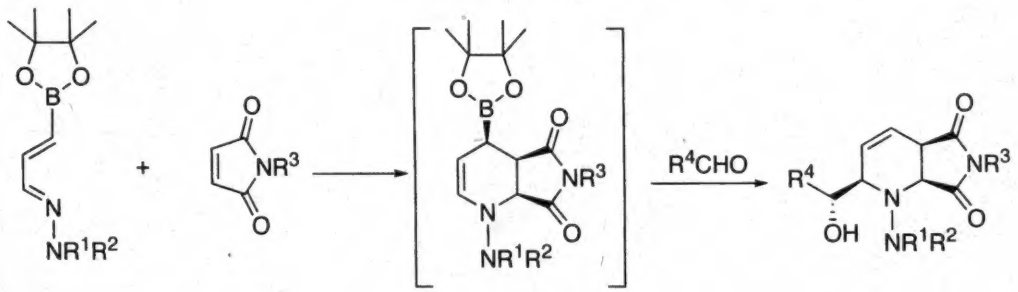
1.4 Three-component hetero-Diels-Alder cycloaddition/allylboration reaction

α-Hydroxyalkyl heterocyclic units are popular components that are present in several classes of biologically active natural products.[9, 26] Consequently, there is significant interest in the development of new methodologies to access this kind of structures. In light of the success of the three-component Diels-Alder cycloaddition/allylboration reactions, a number of novel hetero-Diels-Alder cycloaddition/allylboration variants have been developed and successfully applied in both target-oriented and diversity-oriented synthesis.

1.4.1. Three-component aza-Diels-Alder cycloaddition/allylboration reaction

1.4.1.1 Three-component aza-Diels-Alder cycloaddition/allylboration reaction in solution phase synthesis

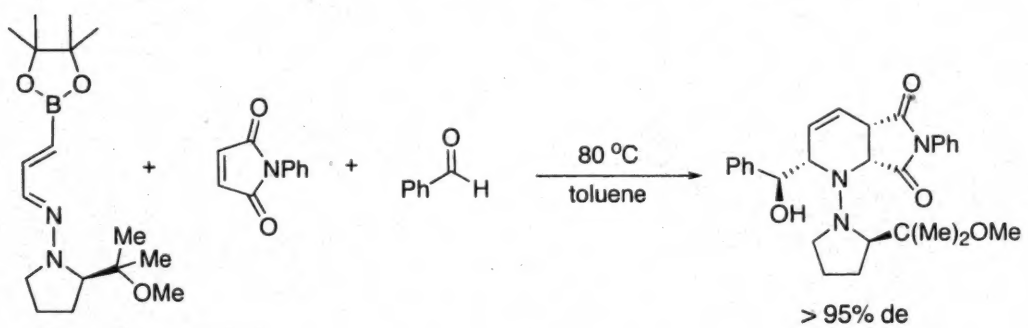
Piperidine alkaloids that embody a β-amino alcohol unit are endowed with a vast range of biological activities.[26] In response to the synthetic challenge presented by these molecules, Hall and co-workers[6a, 6b] have developed a novel three-component hetero-Diels-Alder cycloaddition/allylboration strategy. Similar to the three-component Diels-Alder cycloaddition/allylboration, this strategy involves the formation of transient allylboronate intermediates through hetero-Diels-Alder reactions between 1-aza-4-borono-1,3-butadienes and appropriate dienophiles as the first stage, followed by allylation reaction of the resultant allylboronate with added aldehydes as the final stage (Scheme 1.6).



Scheme 1.6

Different reaction conditions, and different types of substrates were explored in the three-component reaction. Intriguingly, the "one-pot" procedure in which the three reactants are added simultaneously was found to provide better yields of final product as

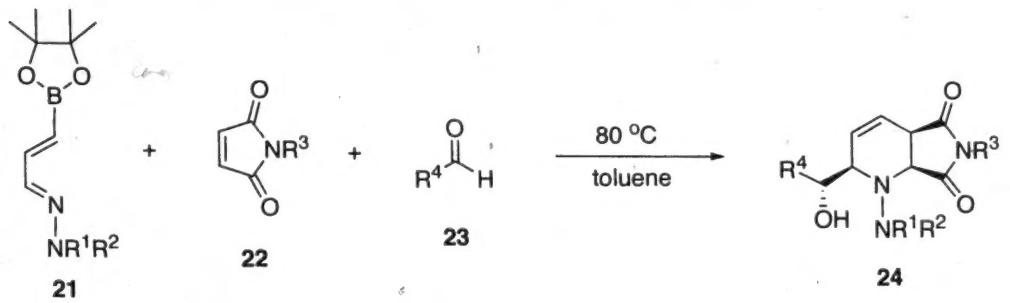
compared to other procedures involving a sequential addition of reagents. When using the more synthetically expensive reagent: the diene, as the limiting component, the reaction yields are generally modest. The efficiency of the reaction, however, is noteworthy considering the ready availability of starting materials as well as the high level of structural change and the stereoselectivity afforded to the products. Alternatively, the product yield improved significantly when excess diene was employed. In term of the substrate scope, while only malemide derivatives are suitable dienophiles, the substrate generality for the hydrazine moieties of the dienes, and the aldehyde substituents are excellent. Overall, a variety of α-hydroxyalkyl piperidine derivatives with four stereogenic centers and four variable groups can be made in modest to good yields with excellent diastereoselectivity (Table 1-3), and this methodology has been utilized by Hall and co-workers[6c] to synthesize piperidine libraries for chemical biology application. Moreover, this method was successfully applied to the preparation of enantiopure bicyclic molecules by using a proline-derived chiral hydrazone (Equation 1-2).



25 **26**

Equation 1-2

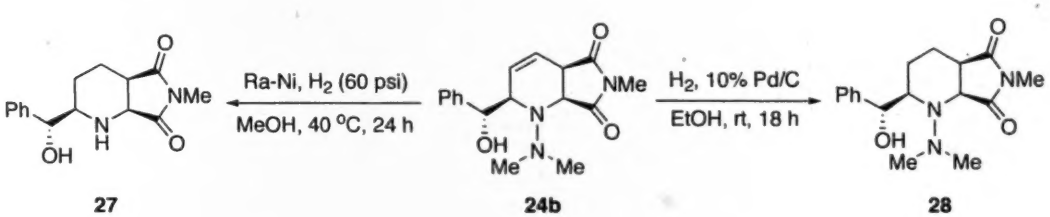
Table 1-3. Three-component aza-Diels-Alder cycloaddition/allylboration reaction[6b]



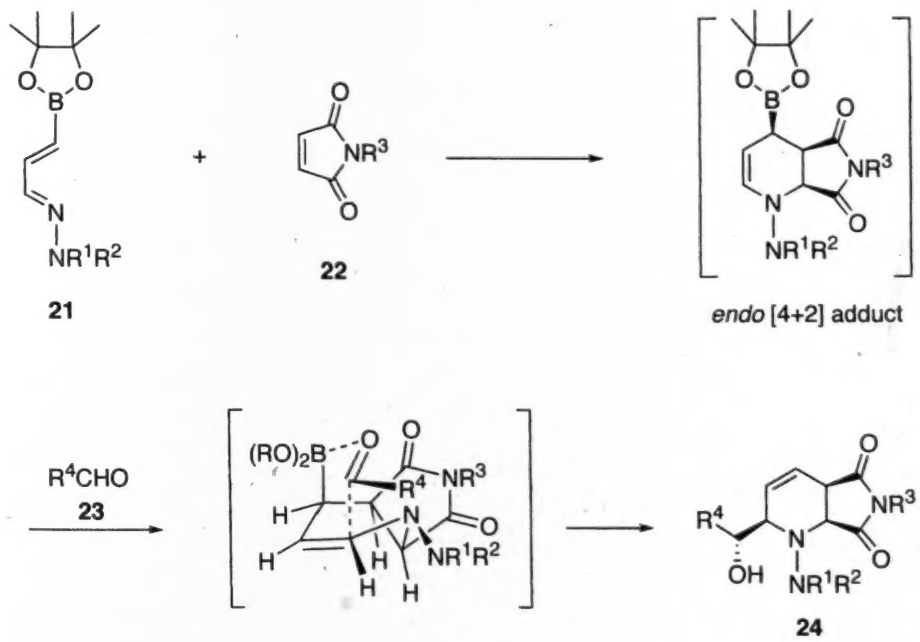
Entry	Diene (R^1, R^2)	Dienophile (R^3)	Aldehyde (R^4)	Product	Yield (%)
1	**21a** (Me, Me)	Ph	Ph	**24a**	64
2	**21a** (Me, Me)	Ph	Ph	**24a**	75
3	**21a** (Me, Me)	Me	Ph	**24b**	50
4	**21a** (Me, Me)	Ph	4-$NO_2C_6H_4$	**24c**	52
5	**21a** (Me, Me)	Ph	4-$MeOC_6H_4$	**24d**	48
6	**21a** (Me, Me)	Me	2-MeC_6H_4	**24e**	50
7	**21a** (Me, Me)	Ph	*i*$PrCH_2$	**24f**	50
8	**21a** (Me, Me)	Me	C_6H_{11}	**24g**	39
9	**21a** (Me, Me)	Me	2,4,6-Me-C_6H_2	**24h**	_
10	**21b** (H, Ph)	Ph	Ph	**24i**	76
11	**21c** (H, 4-$CF_3C_6H_4$)	Me	Ph	**24j**	77
12	**21d** (H, 4-$MeOC_6H_4$)	Me	Ph	**24k**	55
13	**21e** (Me, Ph)	Ph	Ph	**24l**	65
14	**21e** (Me, Ph)	Ph	2-MeC_6H_4	**24m**	68
15	**21f** (H, Ac)	Ph	Ph	**24n**	42
16	**21g** (H, Boc)	Me	Ph	**24o**	61

The bicyclic products could be transformed into the corresponding piperidines by hydrogenation. In addition, the double bond in the bicyclic product could be selectively reduced without cleavage of the hydrazine N-N bond (Scheme 1.7). X-ray

crystallographic analysis of **28** revealed that the relative stereochemistry of the product is the same as that of the carbocyclic series of Vaultier and co-workers. Mechanistically, it is reasonable to assume that the cycloaddition proceeded with complete *endo*-selectivity. From the resulting cyclic allylboronate, the stereochemical outcome of the allylboration step can be rationalized via a cyclic chair-like transition state involving *anti* coordination of the aldehyde to the boronyl group oriented axially on the *endo* face of the piperidine ring (Scheme 1.8).



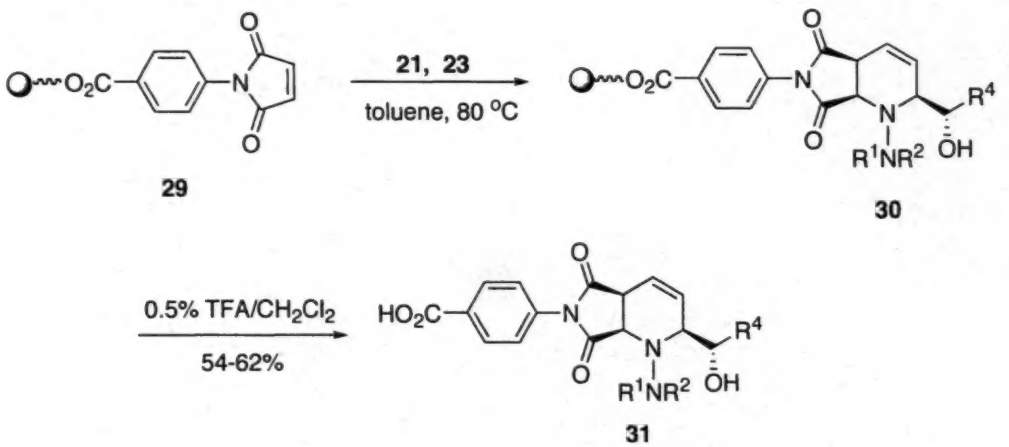
Scheme 1.7



Scheme 1.8

1.4.1.2 Three-component hetero-Diels-Alder cycloaddition/allylboration reaction in solid-phase synthesis

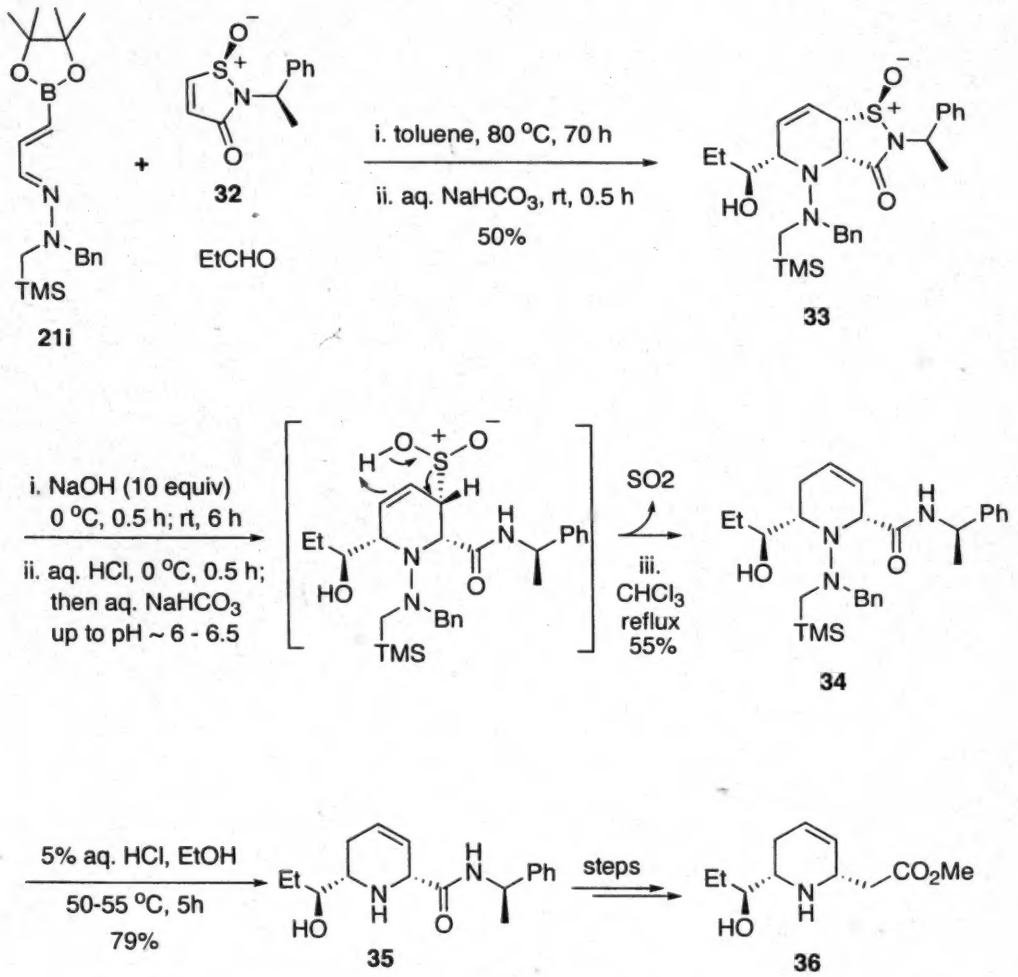
There is tremendous interest in the development of solid supported approaches to synthesize small molecule libraries, particularly those that contain polyfunctional heterocycles. Thus, as a result of their successful efforts with the three-component reaction in solution phase, Hall and co-workers[6b] further extended their strategy to include the use of one solid supported component. To minimize the loss of diversity occasioned by conjugating one of the substrates, SASRIN-*p*-maleidobenzoic acid (MBA) resin was chosen as the solid supported reagent. The optimal procedure involves heating a mixture of a diene (five equivalents), a dienophile and an aldehyde (ten equivalents) in toluene at 80 °C. After completion of the reaction, the product was cleaved from the resin under acidic conditions, and it was obtained with good yield and reasonable level of purity (80-90%) (Scheme 1.9).



Scheme 1.9

1.4.1.3 Applications in natural product synthesis

The three-component aza Diels-Alder cycloaddition/allylboration strategy has been applied to the enantioselective total synthesis of methyl palustramate (**36**) by Hall and co-workers (Scheme 1.10).[6d, 6e] In their synthesis, they used Waldner's chiral sulfinimide **32** as the dienophile to control the absolute stereochemistry of the product. Thus, the three-component reaction between diene **21i**, dienophile **32** and propanaldehyde furnished the heterobicyclic adduct **33** in its enantiopure form with 50% yield. Then, intermediate **33** underwent a retro-sulfinyl-ene reaction in which extrusion of SO_2 occurred concomitantly with a migration of the C4-C5 double bond to the C3-C4 position to afford **34**. The stage was set for testing the hydrazine cleavage strategy. After extensive optimization, it was found that the hydrazine could be selectively cleaved by being stirred in ethanolic aqueous HCl solution to furnish the key intermediate **35**. At the end, **35** was converted to methyl palustramate in several steps. Gratifyingly, the synthesis of methyl palustramate was achieved with merely two purification steps, and in only 10 linear synthetic steps from commercial available starting materials, which clearly demonstrates the power of this three-component reaction in target oriented synthesis.



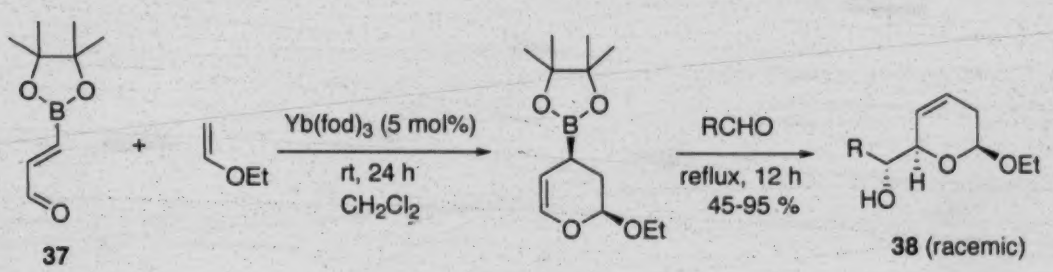
Scheme 1.10

1.4.2 Inverse electron demand hetero-Diels-Alder cycloaddition/allylboration reaction

The inverse electron demand hetero-Diels-Alder reaction between α,β-unsaturated aldehydes and electron-rich alkenes has been known for many years.[27a]

While the thermal cycloaddition usually requires harsh conditions, the variant catalyzed by Lewis acids can be performed under much milder conditions.[27b] Encouraged by the success of the normal electron demand Diels-Alder cycloaddition/allylboration three-component methodologies, we began investigating the suitability of 3-boronoacrolein pinacolate (**37**) in a three-component inverse electron demand hetero-Diels-Alder cycloaddition/allylboration reaction, which could be employed to make synthetically useful α-hydroxyalkyl dihydropyrans.

While we initiated work in this area, an independent study was being carried out by Carreaux and co-workers.[7a] Carreaux and co-workers discovered that $Yb(fod)_3$ was an effective catalyst for the cycloaddition of 3-boronoacrolein (**37**) and ethyl vinyl ether at room temperature. Subsequently, the allylboronate was found to react with a variety of aldehydes in "one pot" to provide racemic α-hydroxyalkyl dihydropyrans in good to excellent yield with excellent diastereoselectivity (Scheme 1-12). The relative stereochemistry of the product was confirmed to be identical to that of the normal electron demand three-component reaction by X-ray crystallographic analysis.



Scheme 1.11

1.5 Thesis objectives

Our group has developed a longstanding interest in the design and application of multicomponent reactions based on the powerful [4+2] cycloaddition/allylboration tandem reaction strategy. In this thesis, our new contribution to the development of the "oxa" variant as well as its application in natural product syntheses will be addressed.

In the normal electron demand Diels-Alder reaction, the bulky electron-withdrawing boronate substituent in the borono-butadiene exerts a strong deactivating effect. Consequently, the thermal cycloaddition works well only with highly electron-poor dienophiles such as *N*-substituted maleimides. This drawback significantly limits the application of this methodology. We sought to examine the effect of electron-donating ether substituents to counterbalance the deleterious effect of the boronate group on the butadiene. This work is discussed in Chapter 2.[28]

Stimulated by recent advances in catalytic asymmetric inverse electron demand hetero-Diels-Alder reactions, we envisioned that 3-boronoacrolein esters could be viable dienes in the asymmetric inverse electron demand Diels-Alder reactions with electron-rich enol ethers catalyzed by chiral Cr(III) complexs.[29] Furthermore, we expected that the resulting chiral boronates would undergo highly diastereoselective allylboration reactions with aldehydes to afford synthetically valuable and enantiopure α-hydroxyalkyl dihydropyran derivatives.[7b] Our work in this area is presented in Chapter 3.

Our ultimate goal in developing a new synthetic methodology is to apply it to the syntheses of bioactive molecules. In the second part of this thesis, two total syntheses employing the catalytic asymmetric inverse electron demand Diels-Alder cycloaddition/allylboration sequence will be described. We first set out to demonstrate the power of the new methodology by a concise total synthesis of the oviposition attractant pheromone of the female *Culex* mosquito,[7b] which is capable of transmitting the West Nile virus. This part is described in Chapter 4.

In response to the increasing demand for new antimicrobial agent, we developed an efficient synthetic route to a member of the potent thiomarinol family of antibiotics.[7c] Based on this route, a number of analogues were synthesized. Optimization of the syntheses as well as the antimicrobial activity of these compounds will be discussed in Chapter 5.

1.6 References.

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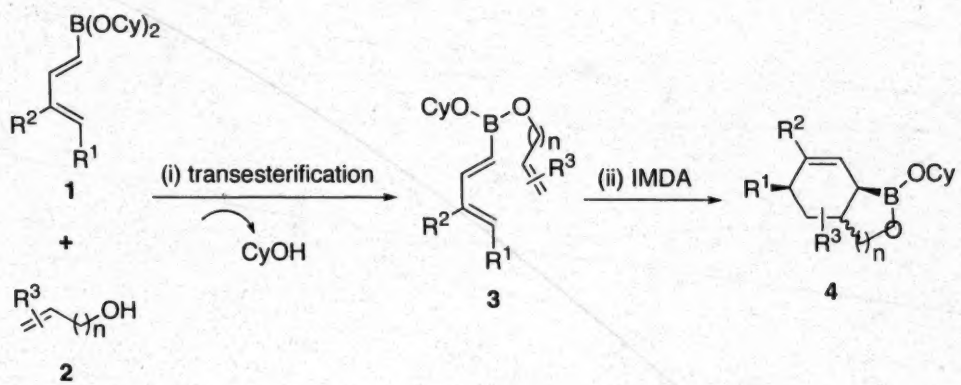
Chapter 2

New Electronically Enriched Boronobutadienes for the Synthesis of Hydroxylated Cyclohexenes via Three-Component Diels-Alder Cycloaddition/Allylboration

2.1 Introduction

In the normal electron demand Diels-Alder reaction, the bulky electron-withdrawing boronate substituent in a boronobutadiene exerts a strong deactivating effect. Consequently, the thermal cycloaddition works well only with highly electron-poor dienophiles such as *N*-substituted maleimides, and harsh conditions were usually required for the reaction to complete. This drawback significantly limits the application of the normal electron demand Diels-Alder cycloaddition/allylboration tandem reaction.

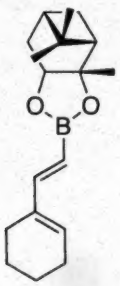
Over the years, a number of approaches have been devised to overcome these limitations. It was hoped that these efforts would lead to improved substrate scope and allow the reaction to be performed under milder conditions. Along this line, Batey and co-workers reported an elegant tandem transesterification/intramolecular [4+2] cycloaddition approach.[2] The general strategy involves first connecting an unsaturated alcohol **2** to the dienylboronates **1** in situ via a transesterification reaction; a C-B-O tethered intramolecular Diels-Alder reaction (IMDA) of intermediate **3** provides the boracycles of type **4**. Since IMDAs are more entropically favoured than their intermolecular counterparts, these reactions usually proceed under milder conditions and allow the use of less activated dienophiles (Scheme 2.1).



Scheme 2.1

According to the FMO theory, increasing the electron density in the diene or decreasing the electron density of the dienophile facilitates the normal electron demand Diels-Alder reaction. As a result, efforts toward expanding the scope of the reaction partners involving 1-boronobutadiene mainly relied on manipulating the electronic properties of the dienes or dienophiles. As described in Chapter **1**, one successful way is to activate the dienophile with a Lewis acid.[3] The coordination of a Lewis acid to the basic site on the dienophile lowers the energy of the LUMO of the dienophile, thus, allowing the reaction to be carried out under milder conditions. In addition to the Lewis acid catalyzed strategy, the opposite strategy, the use of a Lewis base to activate the diene was also explored by several groups. The first example, reported by Wang, involved the use of a dienylboronic acid-diethanolamine adduct as the diene and *N*-phenylmaleimide as its cycloaddition partner.[4] In this diene, the coordination of nitrogen into the empty *p* orbital on boron reduces the delocalization of the π electrons of the diene into the boronate group. As a consequence, the diene becomes more electron-rich than the corresponding "free" boronic esters. In this way, it was found that the replacement of the

diol ligand with a diethanolamine significantly enhanced the intrinsically poor reactivity of the 1-boronobutadiene. For instance, whereas the Diels-Alder reaction between diene **6** and *N*-phenyl maleimide completes within four hours at room temperature, the same reaction involving diene **5** requires ten days under the same reaction conditions (Figure 2-1). A similar activating effect was also observed by my colleague in the Hall laboratory.[5]



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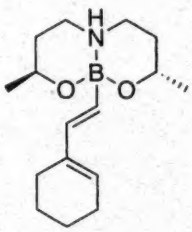
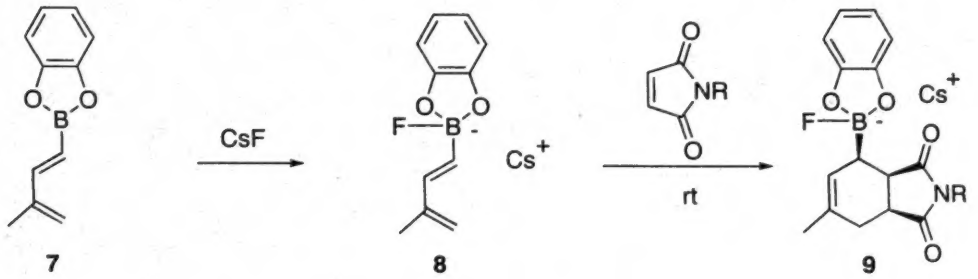


6

Figure 2-1. 1-Boronobutadiene **6** activated by a Lewis base

In another type of reaction involving Lewis base activation, Vaultier and co-workers used the ate complex **8,** which was prepared by addition of a stoichiometric amount of CsF to a solution of **7** as the diene.[6] As a result of the donation of electrons from fluorine to boron, the rate of the cycloaddition involving a number of dienophiles was significantly accelerated (Scheme 2.2). While the Lewis base catalysis is a very effective way to activate 1-boronobutadienes, the tetra-coordinated boron species such as **6** and **9** usually cannot undergo the subsequent desired allylboration reaction. Thus, a three-component reaction variant of this reaction can not be conceived with these types of dienes.



7 8 9

Scheme 2.2

2.2 Our approach

We were interested in developing a three-component variant of this reaction that would operate under mild conditions. Our approach to address the reactivity issue, which will be described in this chapter, involved the design of dienes **10** and **11** (Figure 2-2). We envisioned that an electron-donating ether substituent would counterbalance the deleterious effect of the boronate group, thus improving the reactivity of the diene. In addition, we were also interested in accessing the products of this reaction in their enantioenriched form via chiral Lewis acid catalysis. In principle, the use of diene **10** or **11** in the three-component reaction will allow access to a number of new oxygenated cyclohexene derivatives with a stereodefined hydroxyalkyl substituent.

10 **11**

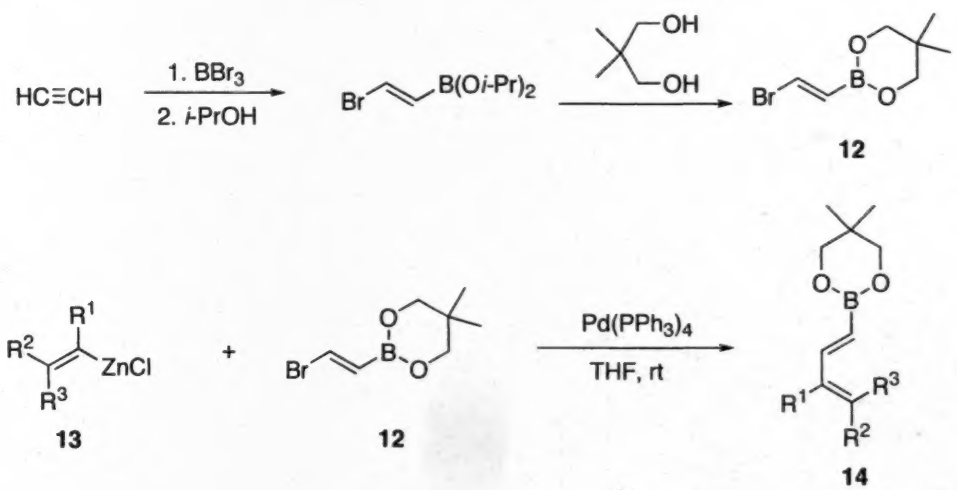
Figure 2-2. 1-Borono butadienes with electron-donating alkoxy substituents

2.3 Background on the synthesis of 1-boronobutadienes

Over the years, a number of methods have been developed to prepare 1-boronobutadienes. Herein, these methods will be reviewed briefly.

2.3.1 Cross-coupling reaction approach

One route to 1-boronobutadienes is the cross-coupling of alkenyl zinc chlorides with *E*-2-bromoethenyldialkoxylboronates (Scheme 2.3). As reported by Suzuki[7a,b] and subsequently by Vaultier,[7c] a variety of functionalized dienylboronates of type **14** can be prepared using this approach. The coupling conditions are mild, and tolerate a wide variety of functional groups. The drawbacks of the route include the limited availability of the alkenyl zinc reagent **13** and the cumbersome preparation of the coupling partner **12**.

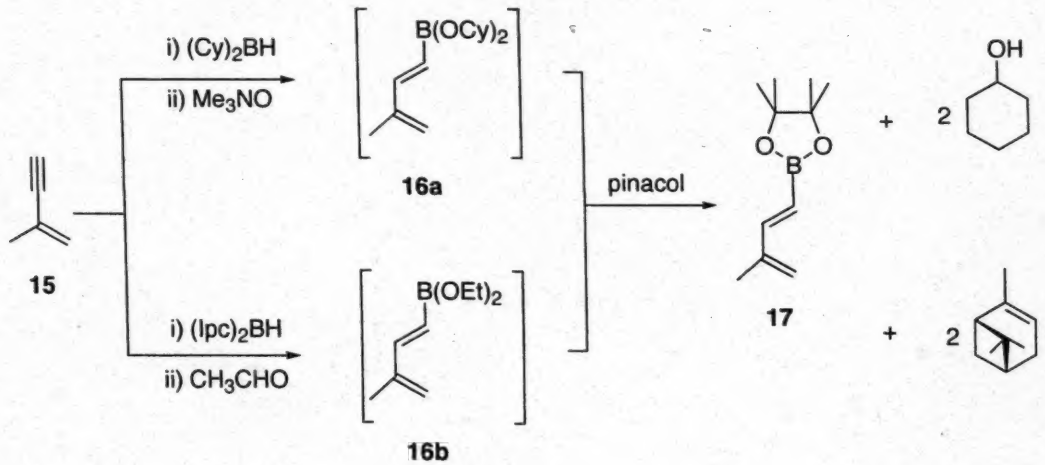


Scheme 2.3

2.3.2 Hydroboration approach

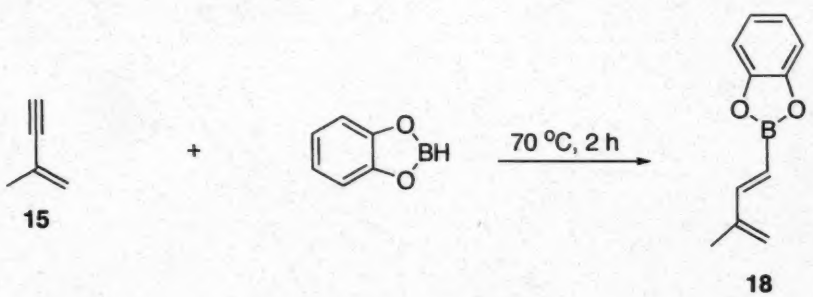
In principal, the methods that have found application in the transformation of simple alkynes into alkenylboronic acids and (or) their derivatives might be employed in the synthesis of 1-boronobutadiene esters. Since alkenylboronic acids are usually made from alkynes through hydroboration reactions, correspondingly, the most popular approach up to date to access 1-boronobutadiene esters is via the hydroboration of an enyne with a suitable hydroborating agent.

Vaultier and co-workers relied on this strategy in their preparation of boronate **17** via the selective hydroboration of enyne **15** with dicyclohexylborane, followed by oxidative dealkylation and transesterification with pinacol (Scheme 2.4). Likewise, the boronate **17** could also be synthesized using diisopinocampheylborane as hydroborating agent and acetaldehyde as oxidant.[1a, 8, 9] Because dialkylboranes are highly active hydroborating agents, hydroborations of enynes are fast and usually can be carried out at a low temperature. However, chemoselectivity may be an issue when complex substrates are employed. Furthermore, two equivalents of non-volatile by-products (eg, cyclohexanol, pinene) are generated in the process. The removal of these impurities is often problematic.



Scheme 2.4

In addition to the above reaction sequence, 1-boronobutadienes can also be prepared directly by hydroboration using dioxaborolanes. For instance, Lallemand and co-workers prepared dienylboronate **18** through the direct hydroboration of enyne **15** with catecholborane in quantitative yield (Equation 2-1).[10] The advantage of this approach is that the experimental operation is simple. However, as a result of the low reactivity of dioxaborolane reagents, the hydroboration reaction is usually carried out at elevated temperatures. In addition, these reaction conditions may not be compatible with the presence of Lewis acid-sensitive functional groups in the substrate.

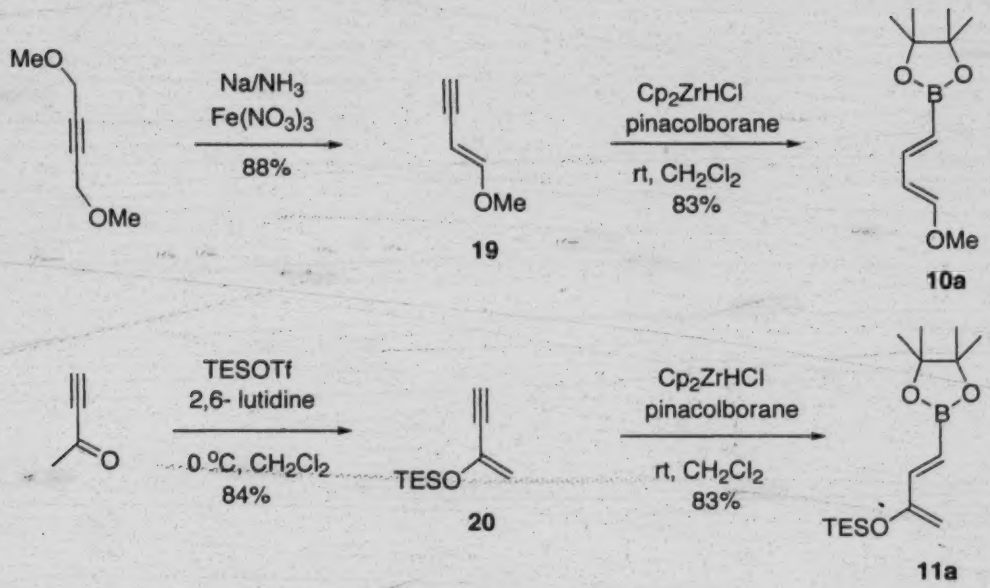


Equation 2-1

2.4 Synthesis of α-hydroxyalkyl cyclohexene derivatives via three-component Diels-Alder cycloaddition/allylboration of diene 11a

2.4.1 Design and synthesis of dienes 10a and 11a

Since the alkyne precursors to these compounds are easy to prepare and pinacol boronates are stable to aqueous workup and chromatography, we set out to synthesize and test model dienes **10a** and **11a** (Scheme 2.5) in the three-component reaction. While the hydroboration of enynes **19** and **20** with dialkylboranes followed by oxidation did not give the desired products, the direct hydroboration with pinacolborane catalyzed by Schwartz' reagent[11] did afford **10a** and **11a** in good yields. These mild hydroboration conditions tolerate a wide variety of functional groups. Therefore, this approach constitutes an extremely valuable method for complex substrates. To our surprise, while this approach has been used for the hydroboration of isolated terminal alkynes for more than ten years, it has never been used to make 1-boronobutadienes. Both dienes **10a** and **11a** can be prepared in gram scale and can be kept safely in the refrigerator (5 °C) for a few weeks without significant decomposition.

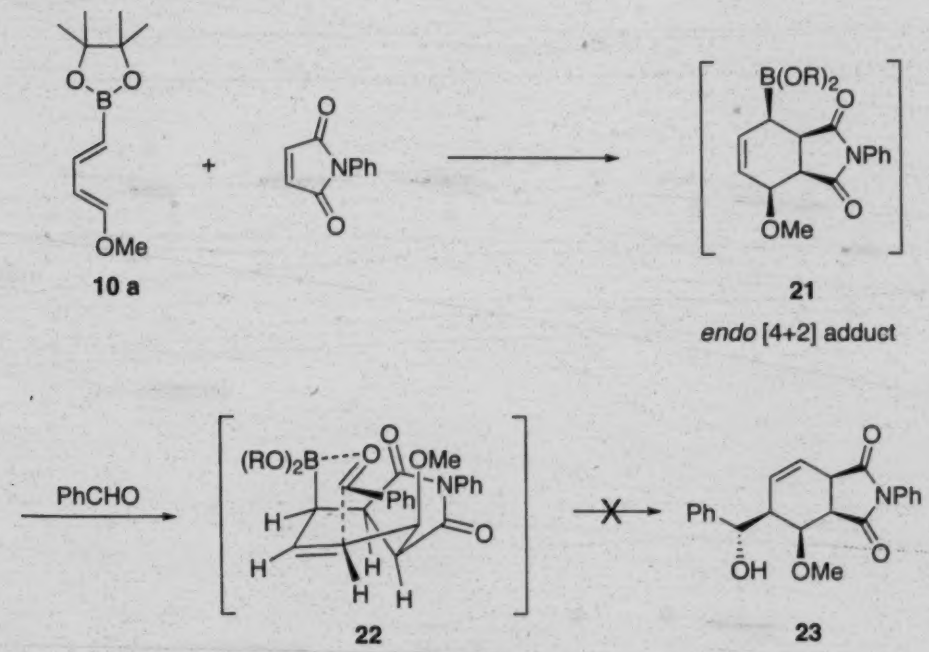


Scheme 2.5

2.4.2 Three-component Diels-Alder cycloaddition/allylboration reactions using dienes 10a and 11a

The 1-boronobutadiene **10a** was first tested in a model "one-pot" Diels-Alder cycloaddition/allylboration protocol involving various dienophiles and benzaldehyde as the aldehyde component. It was found that diene **10a** could undergo the desired cycloaddition with typical dienophiles (maleimides) and provide cycloadducts **21** at relatively high temperature, but the cycloadducts failed to provide allylboration product **23** even at higher temperatures where only decomposition of the starting materials was observed. Furthermore, attempts to promote the allylboration with Lewis acids were not successful.[12] A possible explanation of the failure of the allylboration step is the significant steric crowding caused by the methoxy group on the top (concave) face in the

putative transition structure **22**. The possible occurrence of internal coordination between the methoxy oxygen and the boron atom in the boronate group in the cycloadduct **20** may also inhibit the coordination of the aldehyde substrate, thus preventing the reaction from proceeding (Scheme 2.6).



Scheme 2.6

After the failure of diene **10a** in the attempted three-component reaction, we then turned our attention to testing diene **11a**. Amongst the common dienophiles, maleic anhydride was found to react with diene **11a** to afford the corresponding cycloadduct. However, once again the cycloadduct could not undergo the allylboration reaction to provide the final product. Maleimides, on the other hand, did provide the expected end product from the tandem Diels-Alder cycloaddition/allylboration reaction. Moreover, substrate generality for the aldehyde component is excellent, as shown by the range of

aliphatic and aromatic aldehydes (both electron rich and poor) that provide products **23** in good to excellent yields. The products were isolated as single diastereomers.[13]

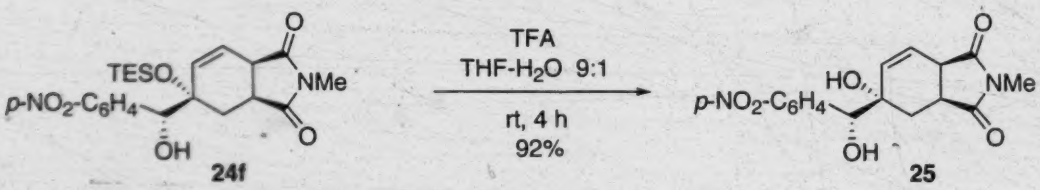
Table 2-1. Three-component Diels-Alder cycloaddition/allylboration of diene **11a**[a]

Entry	Dienophile (R^1)	Aldehyde (R^2)	T (°C)	Time (h)	Product	Yield (%)[b]
1	Ph	C_6H_5	80	16	**24a**	76
2	Ph	4-NO_2-C_6H_4	80	16	**24b**	92
3	Ph	4-MeO-C_6H_4	100	24	**24c**	82
4	Ph	4-Br-C_6H_4	80	16	**24d**	93
5	Ph	i-$PrCH_2$	80	24	**24e**	88
6	Me	4-NO_2-C_6H_4	80	16	**24f**	89
7	Me	4-MeO-C_6H_4	100	24	**24g**	67
8	Me	4-Br-C_6H_4	80	16	**24h**	78

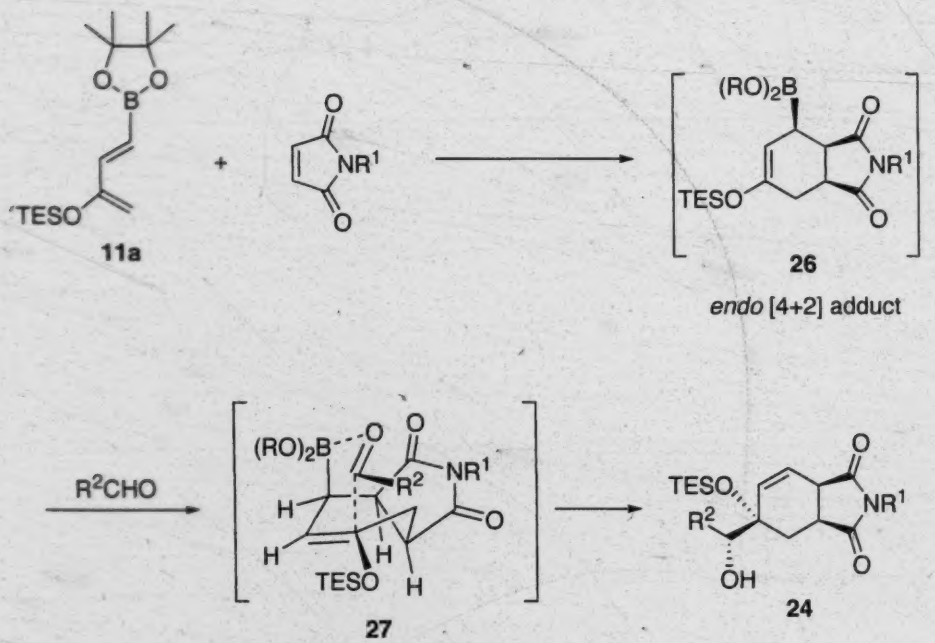
[a] Typical reaction scale: approx. 1.0 mmol diene, 1.1 mmol dienophile, 1.1 mmol aldehyde, 1.0 M in toluene. [b] Yield of isolated, analytically pure product.

The stereochemistry of the final products was determined by X-ray crystallographic analysis of **25**, which was prepared by desilylation of **24f** under acidic conditions (Equation 2-2).[14] The X-ray structure confirmed that the relative stereochemistry in the products of tandem [4+2] cycloaddition/allylboration of diene **11a**, as indicated in **24**, mirrors that of the unactivated 1-boronobutadienes. Mechanistically, the [4+2] cycloaddition of boronobutadiene **11a** with maleimides is expected to proceed

with complete *endo* selectivity to give the allylboronate intermediate **26**. From the latter, the stereochemical outcome of the allylation step can be explained via the usual cyclic chair-like allylboration transition structure **27** involving *anti* coordination of the aldehyde to the boronyl group oriented axially on the *endo* face of the cyclohexene ring (Scheme 2.7).



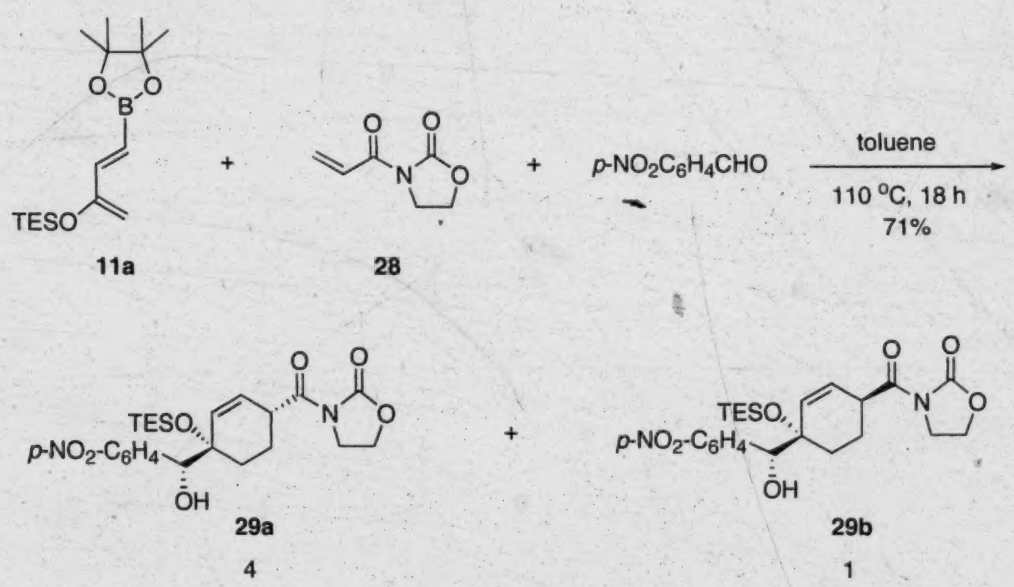
Equation 2-2



Scheme 2.7

Following the optimization of the three-component reaction between maleimides and diene **11a**, we tested the use of mono-activated dienophiles. Although methyl

acrylate reacted with diene **11a** and *p*-nitrobenzaldehyde, it led to a rather poor diastereoselectivity (*endo/exo*, 2:3). All attempts to improve the diastereoselectivity by using various Lewis acids only resulted in decomposition of the diene. The oxazolidinone derivative **28**, however, proved to be effective and provided a better level of selectivity (4:1) and the major isomer was isolated with a 71% yield (Equation 2-3). The structure of the major isomer was tentatively assigned as **29a**.

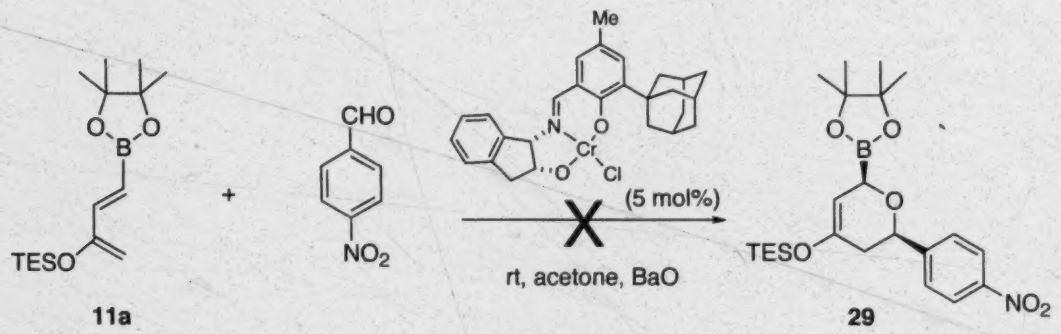


Equation 2-3

2.5 Attempts to use diene 11a in the hetero-Diels-Alder reaction

The hetero-Diels-Alder (HDA) reaction between a diene and an aldehyde is one of the most important ways to synthesize dihydropyran derivatives. The cycloadduct from the HDA reaction of 1-boronobutadiene and an aldehyde could undergo a subsequent allylboration reaction with an added aldehyde to afford highly functionalized

dihydropyran derivatives. The HDA reaction of diene **11a** and 4-nitrobenzaldehyde was tested in the presence of Jacobsen's tridentate Cr (III) catalyst, which has been demonstrated to be an effective catalyst for HDA reactions between moderately activated dienes and simple aldehydes.[15] Unfortunately, no formation of the desired cycloadduct **29** was observed. Raising the temperature of the reaction only resulted in decomposition of the diene (Equation 2-4).



Equation 2-4

2.6 Conclusion

In summary, we have developed an efficient route to electronically enriched 1-boronobutadienes **10a** and **11a**. Although these electronically enriched dienes did not demonstrate the anticipated increase of reactivity to employ moderately activated dienophiles (e.g. acrylates) at low temperatures, the success of the three-component reaction with diene **11a** provides a new stereoselective approach to polysubstituted cyclohexene intermediates with potential use in the synthesis of complex natural products. Moreover, it is noteworthy that dienylboronates **10a** and **11a** are appealing intermediates for potential Suzuki cross-coupling reactions.

2.7 Experimental

2.7.1 General

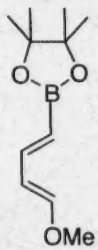
Unless otherwise stated, all reactions were performed under nitrogen atmosphere using flame-dried glassware. Toluene and CH_2Cl_2 were distilled from CaH_2. All aldehydes were purified by bulb-to-bulb distillation prior to use. Analytical thin layer chromatography was performed on Merck Silica Gel 60 F254 plates and were visualized with UV light and 1% $KMnO_4$ (aq). Deactivated silica-gel refers to the silica-gel washed with triethylamine prior to use. NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbon (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dq, doublet of quartets; dd, doublet of doublets; ddd, doublet of doublets of doublets; dddd, doublet of doublets of doublets of doublets; m, multiplet. High resolution mass spectra were recorded by the University of Alberta mass spectrometry service laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra were obtained on a Nicolet Magna-IR 750 with frequencies expressed in cm^{-1}. Melting points were determined in a capillary tube in Gallenkamp melting point apparatus and are uncorrected. Combustion analyses were performed by University of Alberta Micro-Analytical Lab. X-ray crystallography was performed using a Bruker P4/RA/SMART 1000 CCD diffractometer.

2.7.2 Experimental procedures

(*E*)-1-Methoxy-1-butene-3-yne (19)[16]

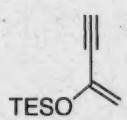
Sodium (1.00 g, 43.0 mmol) was added to liquid ammonia (350 mL) in rbf and the mixture was stirred until a deep blue color persisted. Ferric nitrate hydrate (500 mg, 1.00 mmol) was added and stirring was continued until a uniformly brown color was obtained. Sodium (12.5 g, 0.540 mol) was added to the solution in 1.00 g portions over one hour. 1,4-dimethoxybut-2-yne (25.2 g, 0.220 mol) was added slowly over one hour and the mixture was stirred for another hour. Ether (80 mL) was carefully added and the ammonia was evaporated using a water bath (40 °C). When only traces of ammonia remained, a further 100 mL of ether was added and the mixture was maintained in the water bath until no ammonia evaporation was detectable. Ice-water (150 mL) was added very carefully and the mixture was stirred vigorously until no solid materials remained. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 100 mL). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was distilled off through a 60 cm Vigreux column (bath temperature below 80 °C). The crude product was purified by distillation at reduced pressure (48-50 °C, 70 mmHg) to provide the known product **19** (15.9 g, 88%, *E*/*Z*=9:1). The product should be stored at -5 °C (not stable at rt!). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.95 (d, J = 17.6 Hz, 1H), 4.80 (d, J = 17.6 Hz, 1H), 3.58 (s, 3H), 2.68 (s, 1H).

1-Borono-4-methoxy-1,3-butadiene pinacolate (10a)



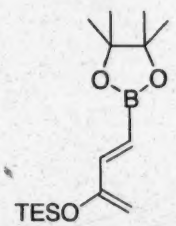
Freshly distilled pinacolborane (2.69 g, 21.0 mmol) and bis(cyclopentadienyl)zirconium chloride hydride (0.510 g, 2.00 mmol) were added to a solution of compound **19** (1.64 g, 20.0 mmol) in CH_2Cl_2 (10 mL) in rbf. The resulting mixture was stirred overnight at ambient temperature, then diluted with ether (40 mL). The ethereal phase was washed with an aqueous saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with ether (40 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash column chromatography (deactivated silica-gel, hexanes) to afford **10a** (3.48 g, 83%) as a colorless oil. IR (neat, cm^{-1}) 2978, 2838, 1644, 1607; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.82 (dd, J = 10.7, 17.6 Hz, 1H), 6.76 (d, J = 12.5 Hz, 1H), 5.60 (dd, J = 10.7, 12.5 Hz, 1H), 5.34 (d, J = 17.6 Hz, 1H), 3.60 (s, 3H), 1.40 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.9, 147.1, 107.7, 82.8, 56.5, 24.8; HRMS (EI, *m/z*) calcd for $C_{11}H_{19}BO_3$ 210.1427, found 210.1429.

2-Triethylsilyloxy-but-1-en-3-yne (20)



To a solution of freshly distilled 3-butyn-2-one (1.02 g, 15.0 mmol) and 2,6-lutidine (3.03 g, 28.0 mmol) at 0 °C in CH_2Cl_2 (15 mL) was added triethylsilyl trifluoromethanesulfonate (4.10 g, 15.5 mmol) dropwise. After stirring at 0 °C for 0.5 hour and at ambient temperature for 0.5 hour, ether (60 mL) was added and the mixture was washed sequentially with water (40 mL), 1N aqueous HCl solution (30 mL), an saturated aqueous $NaHCO_3$ (30 mL) solution and brine (30 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash column chromatography (hexanes/ether 95:5) to afford **19** (2.26 g, 83%) as a colorless oil. IR (neat, cm^{-1}) 3307, 2957, 2913, 2878, 1607; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.68 (s, 2H), 2.82 (s, 1H), 0.98 (t, J = 7.8 Hz, 9H), 0.72 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.6, 103.4, 81.1, 75.1, 6.6, 5.0; HRMS (EI, *m/z*) calcd for $C_{10}H_{18}OSi$ 182.11269, found 182.11273.

1-Borono-3-triethylsilyloxy-1,3-butadiene pinacolate (11a)



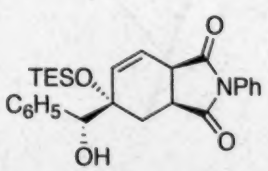
Prepared as described for **10a**. **11a** was obtained as a colorless oil. IR (neat, cm^{-1}) 2957, 2878, 1626, 1588; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.80 (d, J = 17.7 Hz, 1H), 5.86 (d, J = 17.7 Hz, 1H), 4.44 (s, 1H), 4.42 (s, 1H), 1.26 (s, 12H), 0.96 (t, J = 7.8 Hz, 9H), 0.64 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.0, 98.4, 83.2, 24.8, 6.8, 5.0; HRMS (EI, *m/z*) calcd for $C_{16}H_{32}O_3BSi$ 311.2208, found 311.2207.

Synthesis of compound 24a-h

General procedure

To a solution of diene **11a** (0.310 g, 1.00 mmol) in toluene (1 mL) was added aldehyde (1.10 mmol) and dienophile (1.10 mmol) under a nitrogen atmosphere at ambient temperature. The reaction mixture was heated to 80 °C or 100 °C for 16 or 24 hours, then allowed to cool to ambient temperature, diluted with EtOAc (10 mL). A saturated aqueous solution of $NaHCO_3$ (10 mL) was added to the solution and the reaction mixture was stirred for 30 minutes at ambient temperature. The organic layer was then separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to afford **23** as a crude product. The residue was purified by flash column chromatography (EtOAc/hexanes system) to afford **24** (67-93%).

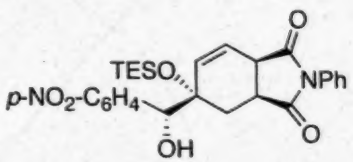
5-(Hydroxy-phenyl-methyl)-2-phenyl-5-triethylsilyloxy-3α,4,5,7α,-tetrahydro-isoindole-1,3-dione (24a).



Mp 155-156 °C; IR (KBr, cm^{-1}) 3489, 3062, 3032, 2953, 2874, 1778, 1708, 1598; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.20-7.48 (m, 10H), 6.10 (dd, J = 4.2, 10.2 Hz, 1H), 5.92 (dd, J = 2.5, 10.2 Hz, 1H), 4.40 (d, J = 3.8 Hz, 1H), 3.60 (ddd, J = 2.5, 4.2, 8.6 Hz 1H), 3.34 (ddd, J = 6.7, 7.5, 8.6 Hz, 1H), 2.46 (d, J = 3.8 Hz, 1H), 2.41 (ddd, J = 6.7, 7.5, 8.6 Hz, 1H), 1.88 (dd, J = 7.5, 13.8 Hz, 1H), 0.84 (t, J = 7.8 Hz, 9H), 0.56 (q, J = 7.8 Hz,

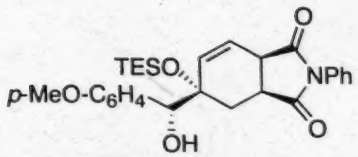
6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.1, 175.2, 139.3, 135.5, 131.7, 129.1, 128.6, 127.9, 127,7, 127.6, 126.3, 123,6, 79.3, 73.7, 40.7, 36.8, 31.0, 7.1, 6.7; HRMS (ESI, *m/z*) calcd for $C_{27}H_{33}NO_4NaSi$ 486.2071, found 486.2079. Anal. calcd for $C_{27}H_{33}NO_4Si$ C, 69.94, H, 7.17, N, 3.02; found C, 69.75, H, 7.30, N, 3.03.

5-[Hydroxy-(4-nitrophenyl)-methyl]-2-phenyl-5-triethylsilyloxy-3α,4,5,7α,-tetrahydro-isoindole-1,3-dione (24b).



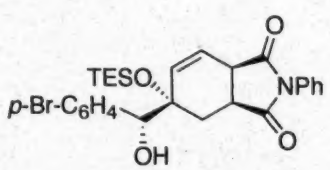
Mp 182-183 °C; IR (KBr, cm^{-1}) 3477, 2954, 2909, 2875, 1778, 1708, 1599; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.24-7.54 (m, 7H), 6.20 (dd, *J* = 4.3, 10.2 Hz, 1H), 5.82 (dd, *J* = 2.3, 10.2 Hz, 1H), 4.46 (d, *J* = 5.4 Hz, 1H), 3.66 (ddd, *J* = 2.3, 4.3, 8.5 Hz, 1H), 3.16 (ddd, *J* = 4.9, 7.8, 8.5 Hz, 1H), 2.65-2.72 (m, 2H), 1.80 (dd, *J* = 7.8, 14.2 Hz, 1H), 0.84 (t, *J* = 7.7 Hz, 9H), 0.58 (q, *J* = 7.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.9, 175.0, 147.4, 146.4, 135.5, 131.6, 129.2, 129.0, 128.7, 126.1, 124.6, 122.6, 78.3, 73.6, 40.5, 36.8, 29.8, 7.1, 6.6; HRMS (ESI, *m/z*) calcd for $C_{27}H_{32}N_2O_6NaSi$ 531.1922, found 531.1922. Anal. calcd for $C_{27}H_{32}N_2O_6Si$ C, 63.76, H, 6.34, N, 5.51; found C, 63.75, H, 6.25, N, 5.40.

5-[Hydroxy-(4-methoxyphenyl)-methyl]-2-phenyl-5-triethylsilyloxy-3α,4,5,7α,-tetrahydro-isoindole-1,3-dione (24c).



Mp 169-170 °C; IR (KBr, cm^{-1}) 3489, 2953, 2909, 2874, 2778, 1710, 1611; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18-7.50 (m, 7H), 6.80 (d, J = 8.8 Hz, 2H), 6.10 (dd, J = 4.0, 10.3 Hz, 1H), 5.96 (dd, J = 2.3, 10.3 Hz, 1H), 4.38 (d, J = 4.9 Hz, 1H), 3.78 (s, 3H), 3.60 (ddd, J = 2.3, 4.0, 8.6 Hz, 1H), 3.32 (ddd, J = 6.9, 7.5, 8.6 Hz, 1H), 2.38 (d, J = 4.9 Hz, 1H), 2.32 (dd, J = 6.9, 13.7 Hz, 1H), 1.88 (dd, J = 7.5, 13.7 Hz, 1H), 0.88 (t, J = 7.7 Hz, 9H), 0.58 (q, J = 7.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.1, 175.2, 159.1, 135,4, 131.7, 131.4, 129.1, 128.9, 128.5, 126.3, 123.6, 113.1, 78.9, 73.8, 55.3, 40.8, 36.8, 31.3, 7.2, 6.7; HRMS (ESI, *m/z*) calcd for $C_{28}H_{35}NO_5NaSi$ 516.2177, found 516.2178. Anal. calcd for $C_{28}H_{35}NO_5Si$ C, 68.12, H, 7.15, N, 2.84; found C, 68.13, H, 7.30, N, 2.83.

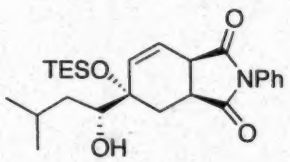
5-[Hydroxy-(4-bromophenyl)-methyl]-2-phenyl-5-triethylsilyloxy-3α,4,5,7α,-tetrahydro-isoindole-1,3-dione (24d).



Mp 145-147 °C; IR (KBr, cm^{-1}) 3484, 3065, 2953, 2909, 2874, 1777, 1708, 1597; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.45 (m, 5H), 7.27 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 8.6 Hz, 2H), 6.14 (dd, J = 4.2, 10.2 Hz, 1H), 5.86 (dd, J = 2.5, 10.2 Hz, 1H), 4.36 (d, J = 5.2 Hz, 1H), 3.62 (ddd, J = 2.5, 4.2, 8.5 Hz, 1H), 3.32 (ddd, J = 6.9, 7.9, 8.5 Hz, 1H), 2.40 (m, 2H), 1.82 (dd, J = 7.9, 13.5 Hz, 1H), 0.86 (t, J = 7.7 Hz, 9H), 0.58 (q, J = 7.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.0, 175.1, 138.2, 135.5, 131.7, 130.6, 129.7,

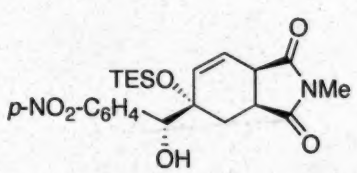
129.2, 128.6, 126.2, 124.0, 121.7, 78.5, 73.5, 40.6, 36.8, 30.4, 7.1, 6.7. HRMS (ESI, *m/z*) calcd for $C_{27}H_{32}NO_4NaSiBr$ 564.1176, found 564.1177. Anal. calcd for $C_{27}H_{32}NO_4SiBr$ C, 59.77, H, 5.95, N, 2.58; found: C, 59.82, H, 5.86, N, 2.57.

5-(1-Hydroxy-3-methyl-butyl)-2-phenyl-5-triethylsilyloxy-3α,4,5,7α,-tetrahydro-isoindole-1,3-dione (24e).



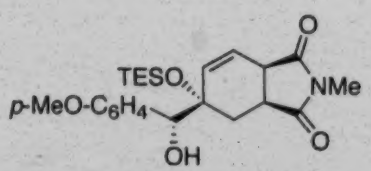
Mp 109-111 °C; IR (KBr, cm^{-1}) 3514, 2954, 2874, 1782, 1711, 1599; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22-7.42 (m, 5H), 6.12 (dd, *J* = 4.0, 10.2 Hz, 1H), 5.96 (dd, *J* = 2.3, 10.2 Hz, 1H), 3.60 (ddd, *J* = 2.4, 4.0, 8.0 Hz, 1H), 3.28 (m, 2H), 2.16 (dd, *J* = 7.4, 13.6 Hz, 1H), 1.96 (dd, *J* = 7.2, 13.6 Hz, 1H), 1.76 (m, 2H), 1.30-1.44 (m, 2H), 0.89-0.96 (m, 12H), 0.83 (d, *J* = 7.6 Hz, 3H), 0.56 (t, *J* = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.3, 175.1, 135.9, 131.7, 129.1, 128.5, 126.3, 123.8, 75.2, 73.6, 40.8, 39.5, 36.8, 30.6, 25.0, 24.1, 21.6, 7.2, 6.8. HRMS (ESI, *m/z*) calcd for $C_{25}H_{37}NO_4NaSi$ 466.2384, found 466.2383. Anal. calcd for $C_{25}H_{37}NO_4Si$ C, 67.68, H, 8.41, N, 3.16; found C, 67.75, H, 8.63, N, 3.09.

5-[Hydroxy-(4-nitrophenyl)-methyl]-2-methyl-5-triethylsiloxy-3α,4,5,7α,-tetrahydro-isoindole-1,3-dione (24f).



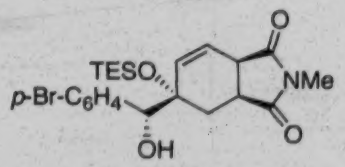
Mp 180-181 °C; IR (KBr, cm^{-1}) 3461, 2954, 2910, 2875, 1776, 1698, 1604, 1519, 1436; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 6.08 (dd, J = 4.3, 10.2 Hz, 1H), 5.78 (dd, J = 2.4, 10.2 Hz, 1H), 4.36 (d, J = 5.5 Hz, 1H), 3.46 (ddd, J = 2.4, 4.3, 8.4 Hz, 1H), 3.18 (ddd, J = 5.7, 7.7, 8.4 Hz, 1H), 3.00 (s, 3H), 2.58 (d, J = 5.6 Hz, 1H), 2.38 (dd, J = 5.7, 14.1 Hz, 1H), 1.76 (dd, J = 7.7, 14.1 Hz, 1H), 0.84 (t, J = 7.8 Hz, 9H), 0.58 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.0, 176.0, 147.4, 146.6, 134.9, 128.8, 124.7, 122.5, 78.3, 73.6, 40.6, 36.7, 30.2, 25.2, 7.0, 6.6; HRMS (ESI, *m/z*) calcd for $C_{22}H_{30}N_2O_6NaSi$ 469.1765, found 469.1766. Anal. cacld for $C_{22}H_{30}N_2O_6Si$ C, 59.17, H, 6.77, N, 6.27; found: C, 59.12, H, 6.70, N, 6.11.

5-[Hydroxy-(4-mthoxyphenyl)-methyl]-2-methyl-5-triethylsilyloxy-3α,4,5,7α,-tetrahydro-isoindole-1,3-dione (24g).



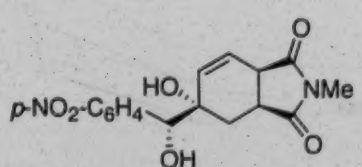
Mp 95-96 °C; IR (KBr, cm^{-1}) 3477, 2953, 2909, 2874, 1775, 1698, 1611, 1584; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.16 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.02 (dd, J = 3.5, 10.3 Hz, 1H), 5.94 (dd, J = 2.1, 10.3 Hz, 1H), 4.16 (s, 1H), 3.68 (s, 3H), 3.40 (m, 1H), 3.16 (m, 1H), 2.96 (s, 3H), 2.18 (s, 1H), 2.04 (dd, J = 8.0, 13.6 Hz, 1H), 1.84 (dd, J = 7.4, 13.6 Hz, 1H), 0.86 (t, J = 7.8 Hz, 9H), 0.44 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.2, 176.2, 159.1, 134.7, 131.5, 128.8, 123.7, 113.1, 79.1, 73.8, 55.3, 40.8, 36.6, 31.6, 25.0, 7.2, 6.7; HRMS (ESI) *m/z* calcd for $C_{23}H_{33}NO_5NaSi$ 454.2020, found 454.2026. Anal. calcd for $C_{23}H_{33}NO_5Si$ C, 64.00, H, 7.71, N, 3.25; found: C, 63.81, H, 7.77, N, 3.25.

5-[Hydroxy-(4-bromophenyl)-methyl]-2-methyl-5-triethylsilyloxy-3α,4,5,7α,-tetrahydro-isoindole-1,3-dione (24h).



Mp 160-161 °C; IR (KBr, cm^{-1}) 3466, 2953, 2909, 2875, 1776, 1698, 1486; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 6.04 (dd, J = 4.1, 10.2 Hz, 1H), 5.84 (dd, J = 2.5, 10.2 Hz, 1H), 4.24 (d, J = 4.8 Hz, 1H), 3.44 (ddd, J = 2.5, 4.1, 8.5 Hz, 1H), 3.16 (ddd, J = 6.9, 7.4, 8.5 Hz, 1H), 2.99 (s, 3H), 2.44 (d, J = 5.0 Hz, 1H), 2.20 (dd, J = 6.9, 13.8 Hz, 1H), 1.80 (dd, J = 7.4, 13.8 Hz, 1H), 0.84 (t, J = 7.8 Hz, 9H), 0.44 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.1, 176.1, 138.2, 134.7, 130.6, 129.5, 124.1, 78.7, 73.6, 40.7, 36.6, 30.9, 25.1, 7.1, 6.6; HRMS (ESI, *m/z*) calcd for $C_{22}H_{30}NO_4NaSi$ 502.1020, found 502.1024. Anal. calcd for $C_{22}H_{30}NO_4Si$ C, 55.00, H, 6.27, N, 2.92; found: C, 54.79, H, 6.09, N, 2.84.

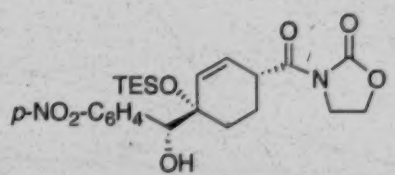
5-Hydroxy-5-[hydroxy-(4-nitrophenyl)-methyl]-3α,4,5,7α,-tetrahydro-isoindole-1,3-dione (25)



A solution of **24f** (92.0 mg, 0.210 mmol) in THF-water-TFA (3:3:1, 1 mL) was allowed to stir at ambient temperature for 3 hours. Then, the solution was diluted with EtOAc (20 mL) and washed with water (5 mL), an saturated aqueous solution of $NaHCO_3$ (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, concentrated

and purified by flash column chromatography (EtOAc) to afford the product **25** (63.0 mg, 92%). IR (CH_3OH, cast, cm^{-1}): 3407, 3113, 1775, 1692, 1605, 1524; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 6.08 (dd, J = 4.0, 10.2 Hz, 1H), 5.78 (dd, J = 2.6, 10.2 Hz, 1H), 4.36 (d, J = 5.5 Hz, 1H), 3.46 (ddd, J = 2.6, 4.9, 8.5 Hz, 1H), 3.18 (ddd, J = 6.9, 8.5, 8.5 Hz, 1H), 2.97 (s, 3H), 2.70 (d, J = 5.6 Hz, 1H), 2.08 (dd, J = 6.9, 13.7 Hz, 1H), 1.76 (dd, J = 8.5, 13.7 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 181.8, 178.8, 149.8, 148.7, 135.4, 130.4, 125.0, 123.4, 78.8, 71.6, 37.3, 31.3, 25.0; HRMS (ESI, *m/z*) calcd for $C_{16}H_{16}N_2O_6Na$ 355.09006, found 355.08996.

3-{4-[Hydroxy-(4-nitrophenyl)-methyl]-4-triethylsilyloxy-cyclohex-2-enecarbonyl}-oxazolidin-2-one (29a).



To a solution of diene **11a** (0.310 g, 1.00 mmol) in toluene (1 mL) was added 4-Nitro-benzaldehyde (0.170 g, 1.10 mmol) and 3-acryloyl-2-oxazolidinone **27** (0.160 g, 1.10 mmol) at under a nitrogen atmosphere at ambient temperature. The reaction mixture was heated to 100 °C for 36 hours, then allowed to cool to ambient temperature, diluted with EtOAc (10 mL), and stirred for 30 minutes with an saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to afford **29** as a crude mixture of diastereomers. The residue was purified by flash column chromatography (EtOAc/hexanes 1:4) to afford

major product **29a** (0.350 g, 71%) as an oil. IR (KBr, cm^{-1}) 3506, 2954, 2875, 1776, 1699, 1604, 1519, 1478; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, J = 8.9 Hz, 2H), 7.44 (d, J = 8.9 Hz, 2H), 5.88 (dd, J = 3.4, 10.3 Hz, 1H), 5.38 (dd, J = 2.1, 10.3 Hz, 1H), 4.58 (s, 1H), 4.41 (t, J = 8.1 Hz, 2H), 4.18 (dddd, J = 2.3, 3.3, 5.5, 5.5 Hz, 1H), 3.98 (m, 2H), 2.08 (m, 1H), 1.96 (m, 2H), 1.78 (m, 1H), 0.86 (t, J = 7.8 Hz, 9H), 0.58 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 153.1, 147.7, 147.2, 133.4, 128.7, 128.4,122.5, 77.8, 75.2, 62.1, 42.9, 39.4, 30.1, 22.7, 7.1, 6.5. HRMS (ESI, *m/z*) calcd for $C_{23}H_{32}N_2O_7NaSi$ 499.1871, found 499.1875. Anal. calcd for $C_{23}H_{32}N_2O_7Si$ C, 57.96, H, 6.77, N, 5.87. found C, 58.04, H, 6.70, N, 5.50.

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Chapter 3

Synthesis of α-Hydroxyalkyl Dihydropyrans via a Catalytic Asymmetric Inverse Electron Demand Hetero-Diels-Alder Cycloaddition/Allylboration Reaction

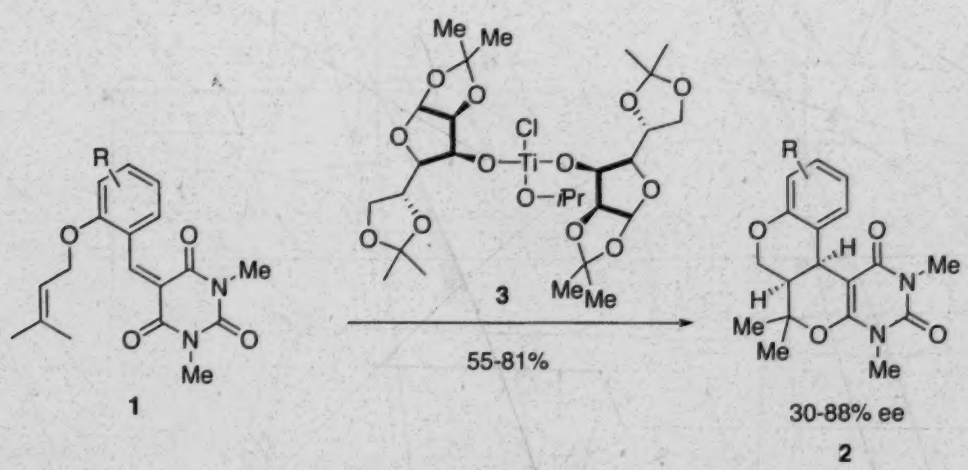
3.1 Introduction

Pyran and dihydropyran units are ubiquitous components that present a wide variety of substitution patterns in several classes of biologically active natural products. Consequently, there is significant interest in the development of synthetic methodologies to access polysubstituted pyran derivatives in optically pure form.[1]

An attractive approach for the preparation of novel optically pure dihydropyran derivatives is via the inverse electron demand hetero-Diels-Alder (HDA) reaction of α,β-unsaturated carbonyls with electron rich alkenes.[2] To control the absolute stereochemistry in the HDA reaction, both chiral auxiliary and asymmetric catalysis approaches were employed. Compared with the auxiliary approach, the asymmetric catalysis approach has several advantages. First, it circumvents the preparation and cleavage steps associated with the auxiliary approach. Second, only substoichiometric amounts of chiral material is required to promote the reaction. Thus, efforts in this area have been devoted mainly to the asymmetric catalysis approach over the past few years.

As a pioneer in the area of inverse electron demand HDA reactions involving 1-oxa-1,3-butadiene and electron rich alkenes, Tietze reported the first example of

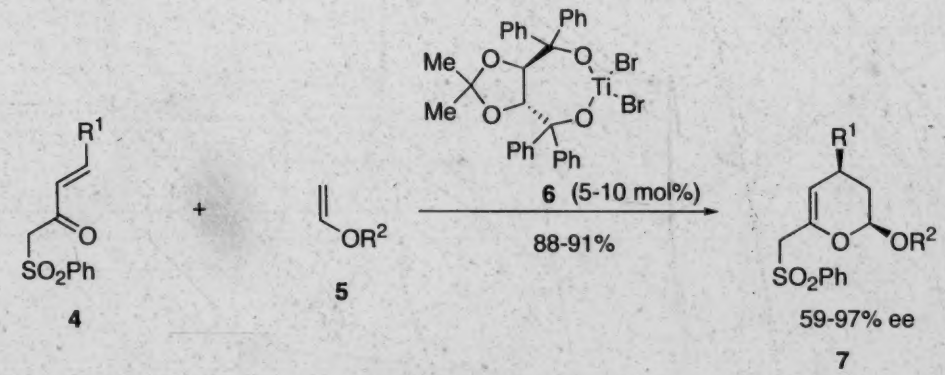
enantioselective inverse electron demand HDA reaction catalyzed by a chiral Lewis acid. This example of intramolecular cycloaddition of heterodiene **1** catalyzed by diacetone glucose-derived titanium (IV) Lewis acid **3** afforded the *endo*-product **2** exclusively in good yield with up to 88% ee (Equation 3-1).[3] The solvent was found to have a profound influence on the enantioselectivity. While the highest enantioselectivity was realized when 1,2,3,5-tetramethyl benzene was used as solvent, a racemate was obtained in chloroform. The reaction was also shown to be temperature-dependent. Whereas the product was formed in 88% ee at 25 °C, a racemic mixture was obtained at 0 °C and 100 °C. The main disadvantage of this reaction is that a stoichiometric amount of the catalyst is required.



Equation 3-1

A chiral titanium (IV) catalyst **6** was also employed in the first example of an intermolecular version of the catalytic enantioselective inverse electron demand HDA reaction.[4] Wada and co-workers demonstrated that the TADDOL – TiX_2 complex **6** catalyzed a highly diastereo- and enantioselective cycloaddition of (*E*)-2-oxo-1-

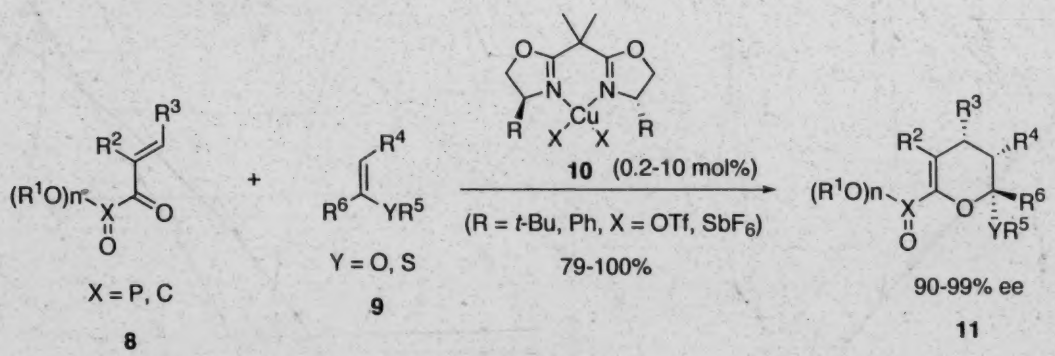
phenylsulfonyl-3-alkenes **4** with enol ethers **5** to provide 2,6-disubstituted dihydropyrans **7** with very good to excellent yield and excellent enantiomeric excess (Equation 3-2). The substituents in both the hetero-diene and the dienophile affect the enantioselectivity and isopropyl vinyl ether was found to be a uniquely effective dienophile. In addition, the choice of halogen ligand in the catalyst is also important to optimize the selectivity. Indeed, the TADDOL – $TiBr_2$ gave better yield and enantioselectivity than its TADDOL – $TiCl_2$ counterpart.



Equation 3-2

The C_2-symmetric chiral BOX – copper(II) complexes **10** have been shown to be effective catalysts for a wide range of important organic addition reactions (e.g., Mukaiyama adol, ene reaction, etc.) where one of the substrates possesses two coordination sites. It was discovered by Evans and JØrgensen that these complexes were also effective catalysts for highly enantioselective inverse electron demand HDA reactions of α,β-unsaturated acyl phosphonates and keto esters **8** with electron-rich alkenes **9** to provide the *endo* adducts **11** with excellent diastereo- and enantioselectiveity (Equation 3-3).[5] The substituent scope for these reactions is quite broad. A variety of

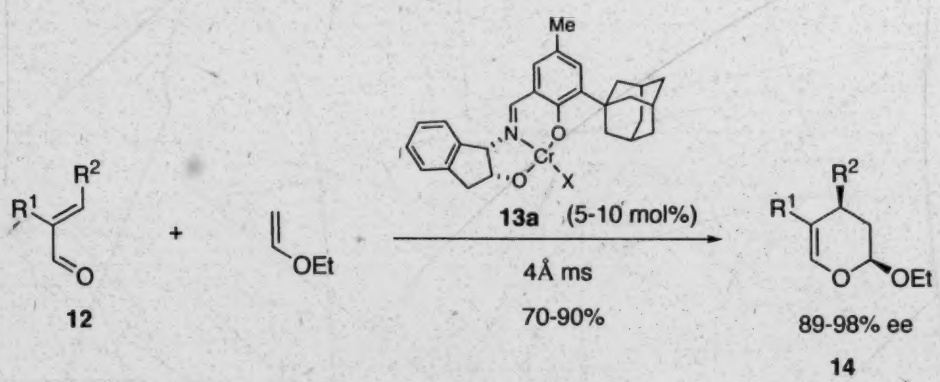
substituents on the diene, such as alkyl, aryl, alkoxy, and thioether substituents are tolerated. Also, acyclic, cyclic, and even trisubstituted enol ethers and sulfides can be used in the HAD reactions. Furthermore, these cycloaddition reactions can be conducted with as low as 0.2 mol% catalyst and are readily carried out on a multigram scale. All these advantages make these reactions particularly attractive from a preparative aspect. In fact, the derived cycloadducts have been transformed into a variety of useful building blocks under different conditions.



Equation 3-3

All successful examples of catalytic asymmetric inverse electron demand HDA reactions discussed above require using a bidentate heterodiene as a reaction partner. The chelation between the catalyst and the heterodiene appears to be essential for attaining good reactivity and stereoselectivity. In the catalytic enantioselective inverse electron demand HDA reactions using heterodienes with a single binding site, the activation and enantiofacial discrimination is controlled by one-point binding of the substrate to the catalyst. Thus, it represents a greater challenge. A real breakthrough in this area occurred in 2002 when Jacobsen and co-workers reported highly enantioselective HDA reactions involving simple α,β-unsaturated aldehydes and ethyl vinyl ethers catalyzed by a

tridentate chromium complex **13**.[6] A wide variety of substituted α, β-unsaturated aldehydes **12** underwent cycloaddition with ethyl vinyl ether with high enantioselectivity (Equation 3-4). Ethyl vinyl ether was found to be the optimal dienophile and the best enantioselectivity was obtained when the reactions were carried out under solvent-free conditions with an excess of ethyl vinyl ether. The derived dihydropyrans **14** have been transformed into a variety of useful chiral building block and this methodology was applied to the total synthesis of iridoid natural products.[7]



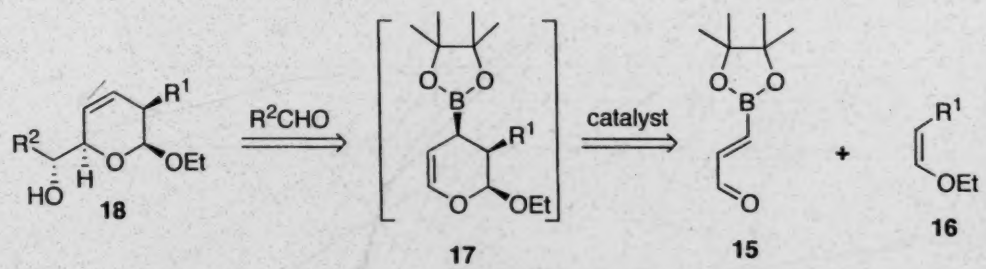
12 **14**

Equation 3-4

3.2 Our proposal

In the normal electron demand Diels-Alder reaction, electron-donating substituents on the diene accelerate the reaction, whereas electron-withdrawing substituents will decelerate it. In the case of inverse electron demand Diels-Alder reaction, the electronic effect of the substituents influences the reactivity in an opposite way. As discussed in earlier chapters, the electron-withdrawing boronate groups in the 1-boronobutadienes exert a significant deactivating effect on the reactivity of the dienes in the normal-electron-demand Diels-Alder reactions. On the other hand, adding a boronate

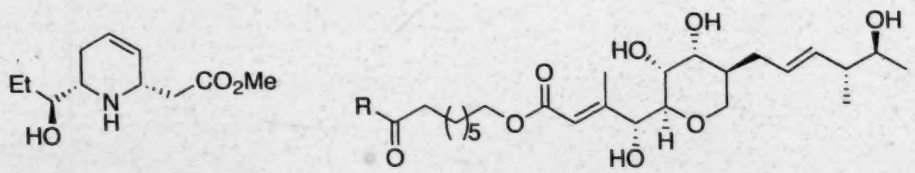
substituent to a diene should increase its reactivity in an inverse electron demand Diels-Alder reaction. This theoretical prediction stimulated us to study the possibility of developing a catalytic asymmetric three-component inverse electron demand hetero-Diels-Alder cycloaddition/allylboration reaction using 3-boronoacrolein pinacolate (**15**) as the hetero-diene (Scheme 3.1). We envisioned that 3-boronoacrolein pinacolate (**15**) could be a viable substrate in the catalytic enantioselective inverse electron demand HDA reaction with enol ethers of type **16** in the presence of an effective chiral Lewis acid catalyst. The intermediate chiral cyclic allylboronate **17** could further react with an aldehyde in a sequential fashion to provide the α-hydroxyalkyldihydropyran **18** as the final product. The allylboration step was expected to be diastereospecific relative to the stereochemistry of the allylboronate.



Scheme 3.1

In principle, this methodology would allow access to α-hydroxyalkyl dihydropyrans in their optically enriched form, which could be further functionalized to provide a variety of useful synthetic intermediates. In fact, a number of biologically interesting natural products, such as (5*R*,6*S*)-6-acetoxy-5-hexadecanolide, (the oviposition attractant pheromone of the female *culex* mosquito,[8] which is capable of transmitting the West Nile virus[9]) as well as the thiomarimol[10] class of marine antibiotics,

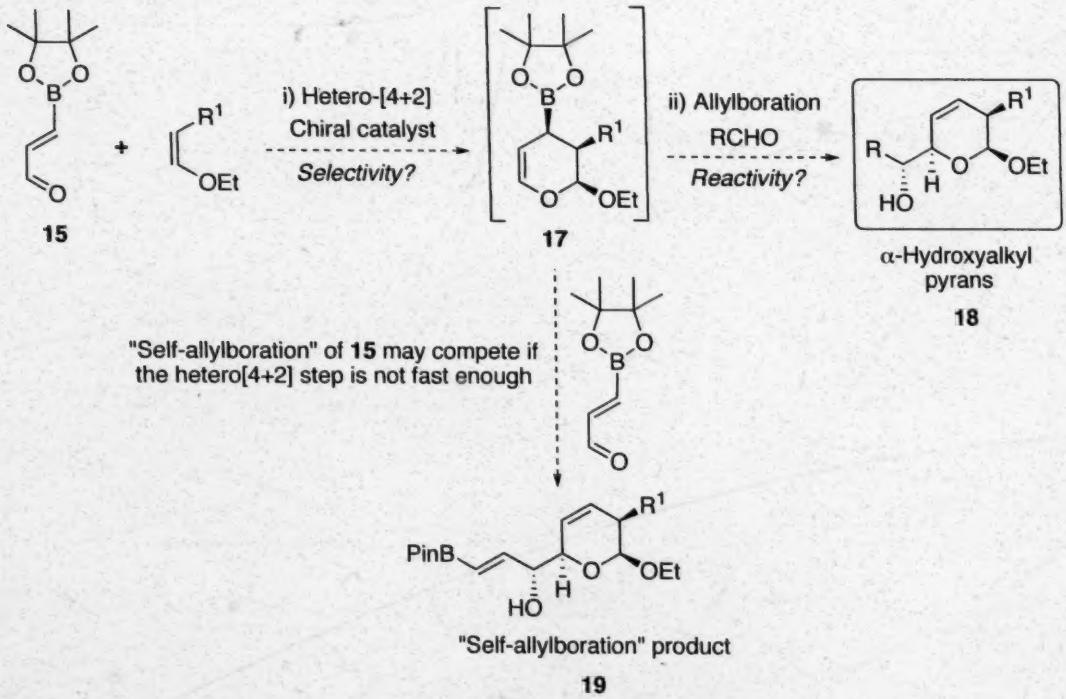
possess such a structural motif (Figure 3-1). This was another important driving force for us to develop the catalytic asymmetric inverse electron demand hetero-Diels-Alder cycloaddition/allylboration methodology.



(-)-methyl palustramate thiomarinols

Figure 3-1. Selected examples of bioactive natural products containing α-hydroxyalkyl dihydropyran units

To develop such a methodology, several issues had to be addressed (Scheme 3.2). First, an effective catalyst for the enantioselective HDA reaction needed to be identified. In addition to controlling the enantioselectivity, the catalyst has to be active enough for the rate of the HDA reaction between **15** and **16** to be much faster than that of the allylboration step in order to prevent the "self-allylboration" reaction between the cycloadduct **17** with **15**. Moreover, the efficiency of the allylboration step was another uncertain aspect.



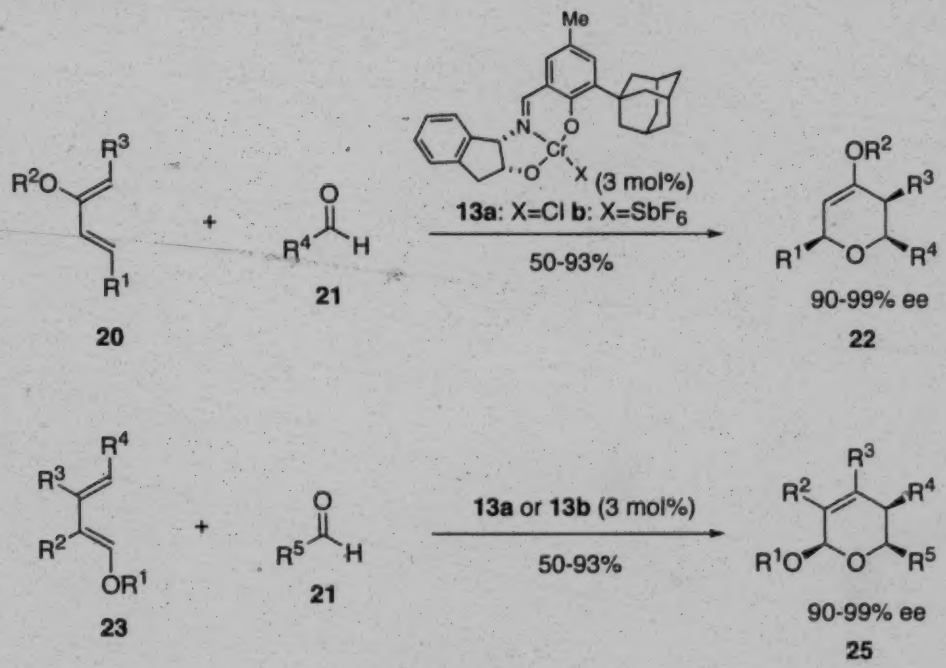
Scheme 3.2

3.3 Catalytic enantioselective hetero-Diels-Alder cycloaddition/allylboration reaction using ethyl vinyl ether as dienophile.

3.3.1 Optimization of the hetero-Diels-Alder step.

When we started this project in early 2002, no example of catalytic enantioselective inverse electron Diels-Alder reaction involving simple α,β-unsaturated aldehydes and enol ethers had been reported in the literature. Our first objective was to find a promising catalyst. After surveying a number of papers dealing with catalytic asymmetric normal electron demand hetero Diels-Alder reactions of aldehydes, the chiral

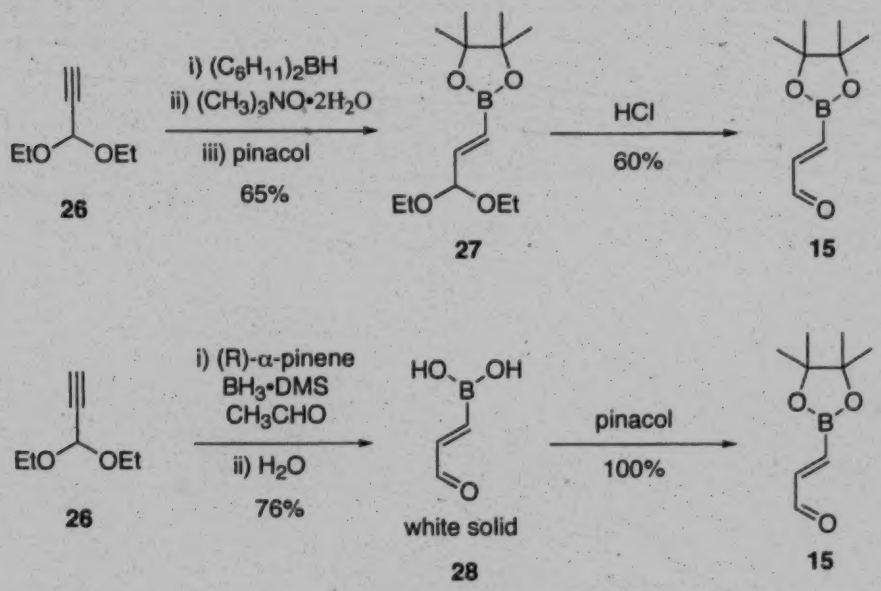
tridentate Cr(III) catalyst **13** developed by Jacobsen and co-workers attracted our attention. This catalyst effectively catalyzes the highly diastereo- and enantioselective HDA reactions between mono-oxygenated 1,3-dienes **20** and **23** and simple aldehydes **21** (Scheme 3.3).[11] The reasons for choosing this catalyst lie not only in its ability for enantiofacial discrimination, but also in its high activity, which is very important in our system. During the course of our study, Jacobsen and co-workers reported that catalyst **13** effectively catalyzed the enantioselective inverse electron demand HDA reactions between α,β-unsaturated aldehydes and ethyl vinyl ether.[6] In this study, authors developed a more practical synthetic route to the catalyst. More importantly, the catalyst was prepared in a better quality by the new procedure, and gave better enantioselectivity than did the catalyst prepared by the original procedure. It was also found that catalyst **13** exists as a dimeric structure, bridged through a single water molecule and bearing one terminal water ligand on each chromium center in the X-ray structure. It is also believed that the dimeric structure is maintained in the catalytic cycle based on preliminary solution molecular weight and kinetic studies. Dissociation of a terminal water molecule to open a coordination site for coordinating with the aldehyde substrate is required for the catalytic cycle. Thus, the presence of a dehydrating agent is crucial for the reaction to proceed. In fact, no cycloaddition is observed in the absence of a dehydrating agent.



Scheme 3.3

With this catalyst **13a** in hand, we decided to try the catalytic HDA reaction of 1-boronoacrolein pinacolate (**15**) using commercially available and cheap ethyl vinyl ether as a dienophile. The preparation of the aldehyde **15** was thoroughly studied by our group. The first route employed by Tailor was a literature procedure involving two consecutive distillations (Scheme 3.4).[12] The whole process proved rather cumbersome and low yielding. It was believed that the aldehyde **15** was thermally unstable and a significant amount of aldehyde decomposed during distillation. To improve the synthesis, Touré and Gravel developed a simpler and more practical procedure that avoids any distillation (Scheme 3.4). In this procedure, the boronic acid **28** was obtained as a white solid in high purity and the ester **15** was easily obtained by reaction with an equimolar amount of

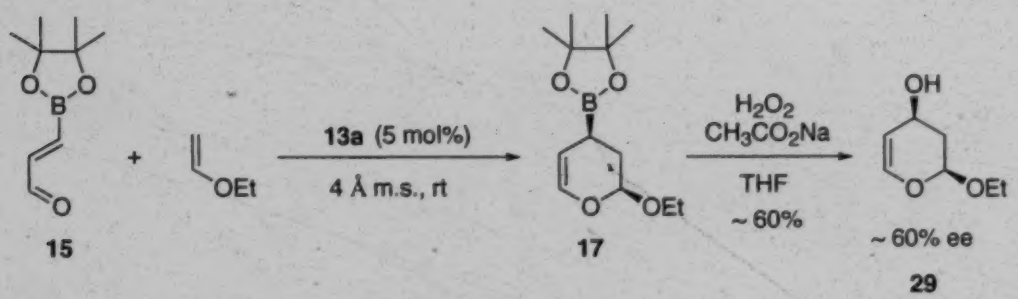
pinacol.[13] The new procedure was successfully applied to the preparation of 1-borono aza dienes used in the three-component aza Diels-Alder cycloaddition/allylboration reaction.



Scheme 3.4

The aldehyde was thus prepared according to the distillation-free procedure and then subjected to the inverse electron demand HDA reaction with ethyl vinyl ether. The reaction was carried out under solvent-free conditions with excess ethyl vinyl ether (nine equivalents) in the presence of 5 mol% Jacobsen's Cr(III) catalyst **13a** and 4 Å molecular sieves at ambient temperature. We were pleased to observe the formation of the desired cycloadduct **17** by ^{1}H-NMR spectroscopy and none of the self-allylboration product. The absence of the self-allylboration product implies that the Cr(III)-catalyzed HDA cycloaddition is significantly faster than the allylboration reaction between the cycloadduct **17** and the aldehyde **15**. After the completion of the reaction, the cycloadduct **17** was directly oxidized with H_2O_2 to provide the secondary alcohol **29** with

retention of stereochemistry (Scheme 3.5).[14] Disappointingly, the alcohol **29** was only obtained with moderate yield and enantioselectivity. Although extensive optimization was conducted by varying reaction parameters including temperature, catalyst loading and dehydrating agent, the ee of the product remained moderate and the results were not consistent.

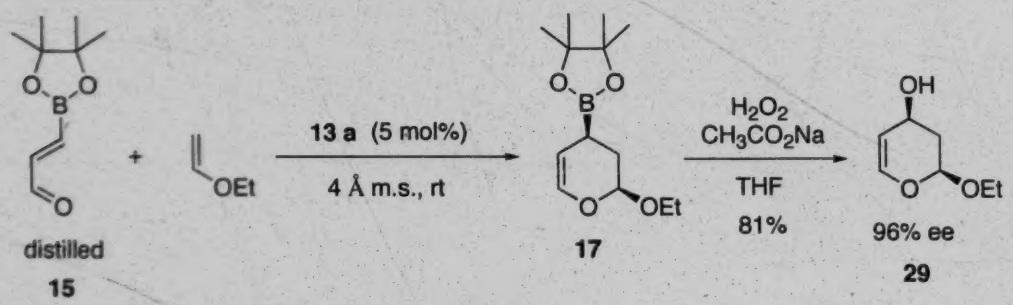


15 **17** **29**

Scheme 3.5

At that stage, we realized that the quality of the aldehyde is critical. We suspected that the aldehyde might be contaminated with a small amount of either boronic acid or pinacol, a situation which could affect the efficiency of the catalyst and result in a low ee of the product. We first tried to purify the aldehyde by column chromatography. However, it was found that the aldehyde was not stable on silica gel. As a result, we had to resort to distillation, which was demonstrated to be low yielding. The crude aldehyde made by condensation of the boronic acid (1 equivalent) and pinacol (1 equivalent) was subjected to bulb-to-bulb distillation at 100 °C and 1 mm Hg. To our surprise, the pure aldehyde was obtained in 94% yield starting from the boronic acid. The purified aldehyde was then subjected to the HDA reaction in neat ethyl vinyl ether in the presence of 5 mol% Jacobsen's Cr(III) catalyst and 4 Å molecular sieves at ambient temperature (23 °C). After oxidation, the secondary alcohol **29** was obtained in 81% yield and 96% ee

(Scheme 3.6). Interestingly, the ^{1}H NMR spectrum of the aldehyde **15** purified by distillation showed no noticeable difference from that of the crude aldehyde before distillation. Yet, the use of distilled **15** was essential for the enantioselectivity.



Scheme 3.6

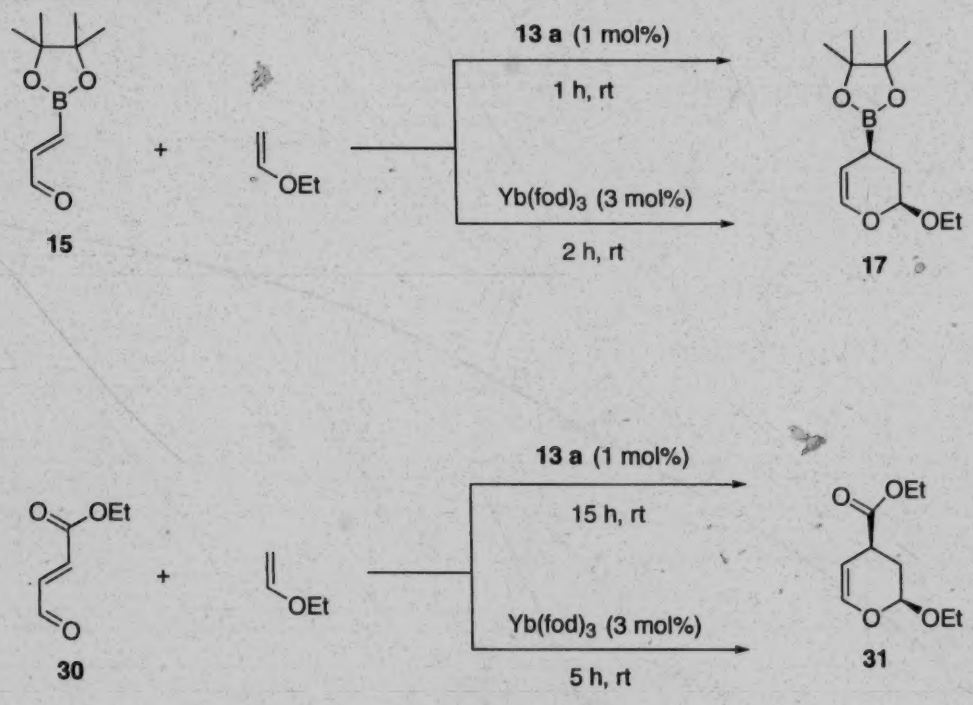
The reaction temperature has a great influence on the conversion and enantioselectivity of the HDA reaction. The reaction was found to be very slow at 0 °C. However, when the reaction temperature is above 23 °C, the enantioselectivity of the cycloaddition decreases. Therefore, the optimal temperature for the reaction is between 20 to 23 °C. The quality of the catalyst is also important for the enantioselectivity. The catalyst **13a** prepared according to the second generation procedure gave a better enantioselectivity (96% ee) compared to the catalyst prepared by the first generation procedure (91% ee).

In addition to 4 Å molecular sieves, we also tested other dehydrating agents. It was found that the enantioselectivity was equally high with BaO instead of molecular sieves. Our next goal was to reduce the catalyst loading and we were glad to observe that both the yield and the enantiomer excess remained very high with as low as 0.3 mol% catalyst when using BaO as dehydrating agent. When using 4 Å molecular sieves as

dehydrating agent, the lowest catalyst loading found to be practical is 0.5 mol%. Further reduction of catalyst loading slowed the cycloaddition reaction and allowed the competitive formation of a significant amount of side product of type **19** (cf. Scheme 3.2) from the allylboration between **17** and aldehyde **15**. The difference between the drying agents could be attributed to their different dehydrating abilities. In comparison with the loading values of 5-10 mol% previously reported by Jacobsen and co-workers for a wide range of α,β-unsaturated aldehydes, this result suggests that 3-boronoacrolein pinacolate is a particularly favorable heterodiene in this reaction.

3.3.2 A [5+2] transition state may account for the exceptional reactivity of 3-boronoacrolein pinacolate.

To explore the influence of the boronate substituent on the reactivity of the heterodiene, we compared the reactivity of 3-boronoacrolein pinacolate **15** in the HDA reaction with ethyl vinyl ether with that of ethyl (*E*)-4-oxobutenoate (**30**) in the presence of either Cr (III) catalyst or $Yb(fod)_3$ (Scheme 3-7). With both catalysts, the rate of the cycloaddition of 3-boronoacrolein (**15**) is several times faster than that of the (*E*)-4-oxobutenoate (**30**) (Figure 3-2). As it is known that vinyl boronates are less reactive than methyl acrylate in the normal electron demand Diels-Alder reaction with cyclopentadiene, the superior reactivity of aldehyde **15** cannot be explained solely by the electron-withdrawing ability of the boronate group.



Scheme 3.7

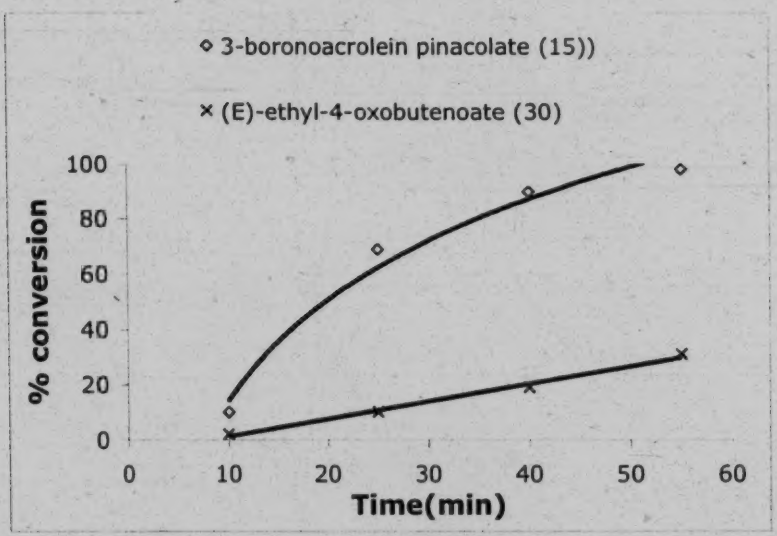


Figure 3-2. Comparative studies of the cycloaddition rates of **15** and **30** with ethyl vinyl ether catalyzed by 1 mol% **13a**

In their studies of Diels-Alder reactions involving vinylboranes as dienophiles, Singleton and co-workers conducted quantum mechanical calculations for the transition state of vinylborane with butadiene and the analogous transition state for vinyldimethylborane to explain the high reactivity, regioselectivity and the endo-stereoselectivity of these dienophiles. Unexpectedly, the calculations show that [4+3] transition structures are responsible for the reactivity and selectivity in these [4+2] reactions.[15] In these transition structures, the boron atom binds significantly to the terminal carbon atom of the diene, and the distances from the terminal carbon of butadiene to the boron atom are less than those to the α-carbon of the vinylborane. In a similar fashion, a [5+2] transition state can be proposed to explain the exceptional reactivity of the 3-boronoacrolein pinacolate in the inverse electron demand HDA reaction (Figure 3-3).

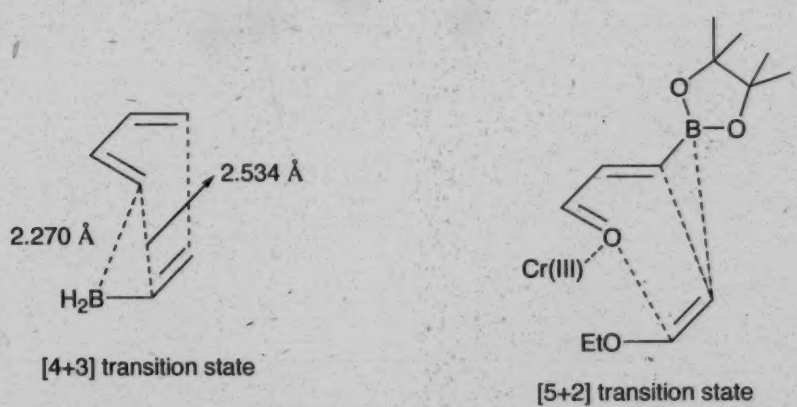
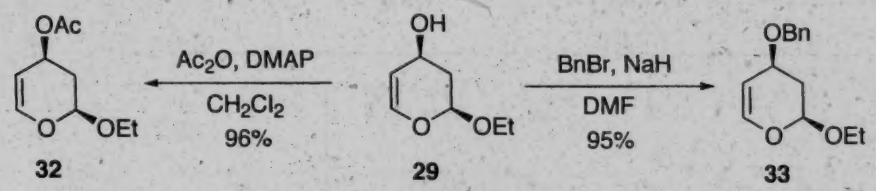


Figure 3-3. Proposed transition state to rationalize the exceptional reactivity of 3-boronoacrolein pinacolate in the HDA reaction

Synthetically, aldehyde **15** also serves as a valuable surrogate of 3-acyloxyacroleins, which were reported to afford the useful 4-hydroxy dihydropyran

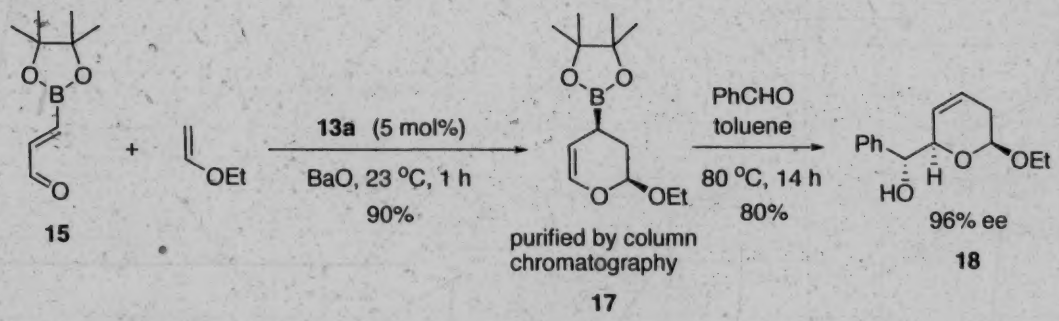
derivatives with a lower selectivity (89% ee). Here, intermediate **29** was isolated in 81% yield with 96% ee from the HDA/oxidation reaction. Routine transformations of the hydroxyl group in **29** led to other intermediates potentially useful in allylic substitution chemistry (Scheme 3.8).[16]



Scheme 3.8

3.3.3 Optimization of the allylboration step.

Following optimization of the HDA reaction, the second step in the three-component sequence, allylboration, was tested using benzaldehyde. To this end, HDA adduct **17** was first isolated and purified using a short column of silica gel. After purification, the cycloadduct was reacted with benzaldehyde in toluene for 14 hours at 80 °C to furnish the corresponding α-hydroxyalkyl dihydropyran in good yield (80%) and excellent diastereoselectivity (>98% de, by ^{1}H-NMR) (Scheme 3.9). The enantiomeric excess of the final α-hydroxyalkyl dihydropyran was measured by chiral HPLC analysis and proved to be the same value as that of the starting allyl boronate **17**.



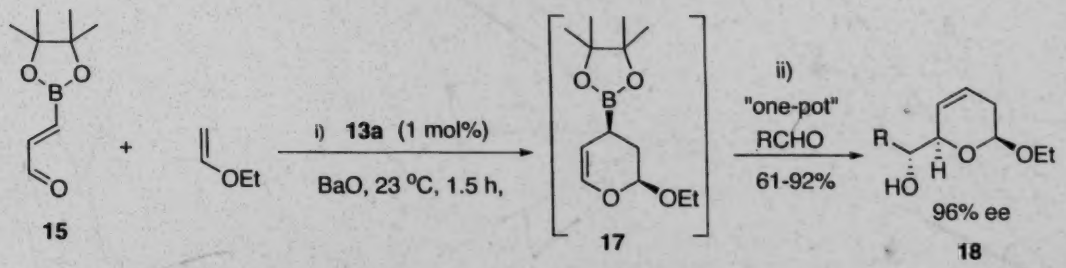
Scheme 3.9

Ideally, these sequential reactions could be performed in "one-pot" to improve the operational simplicity. We were pleased to find that it was not necessary to purify the intermediate **17** and eliminate the residual catalyst when only 1 mol% catalyst was utilized. Thus, the HDA/allylboration sequence can be carried out in a "one-pot" procedure by simple addition of the aldehyde after completion of the cycloaddition step.[17] Allylboration reactions are usually carried out in non-coordinating solvents such as DCM or toluene. To our surprise, we found that the reactivity of allylboronate **17** was not attenuated when using ethyl vinyl ether as solvent. This observation, however, is consistent with a limited study with allylboronic acid 1,3-propanediol ester and benzaldehyde, which showed that polar weakly coordinating solvents gave the fastest rate (THF < toluene < dichloromethane < ethyl ether). [18]

As detailed in Table 3-1, suitable aldehyde substrates for the allylboration step include aromatic aldehydes with different electronic characteristics, and aliphatic aldehydes including functionalized ones such as $TBDMSOCH_2CHO$. All of these different aldehydes afforded dihydropyran products in high yield. Reactions with α,β-

unsaturated aldehydes required a change of solvent to dichloromethane in order to avoid a competing HDA reaction with ethyl vinyl ether. It was found that the concentration of the two allylboration reaction partners had a great impact on the reaction rate. Not surprisingly, the temperature for the allylboration reaction could be reduced or the reaction time could be shortened when the allylboration reaction was conducted without solvent. These mild conditions can in turn suppress side reactions and provide the desired product usually in a better yield. This procedure is especially valuable when the aldehyde is less reactive. For example, when the allylboration between the cycloadduct **17** and tiglic aldehyde was conducted in DCM at a 1.0 M concentration, it was necessary to heat the mixture to 60 °C for 48 h and the product was obtained in only 61% yield. However, when the reaction was carried out under solvent free conditions, the required temperature was reduced to 50 °C and the yield was improved to 76%. A main limitation of the solvent free procedure is that the aldehyde has to be a liquid at the reaction temperature. Disappointingly, attempts to accelerate the allylboration step by Lewis acids were not successful.

Table 3-1. Substrate scope for the catalytic enantioselective three-component HDA cycloaddition /allylboration reaction[a]

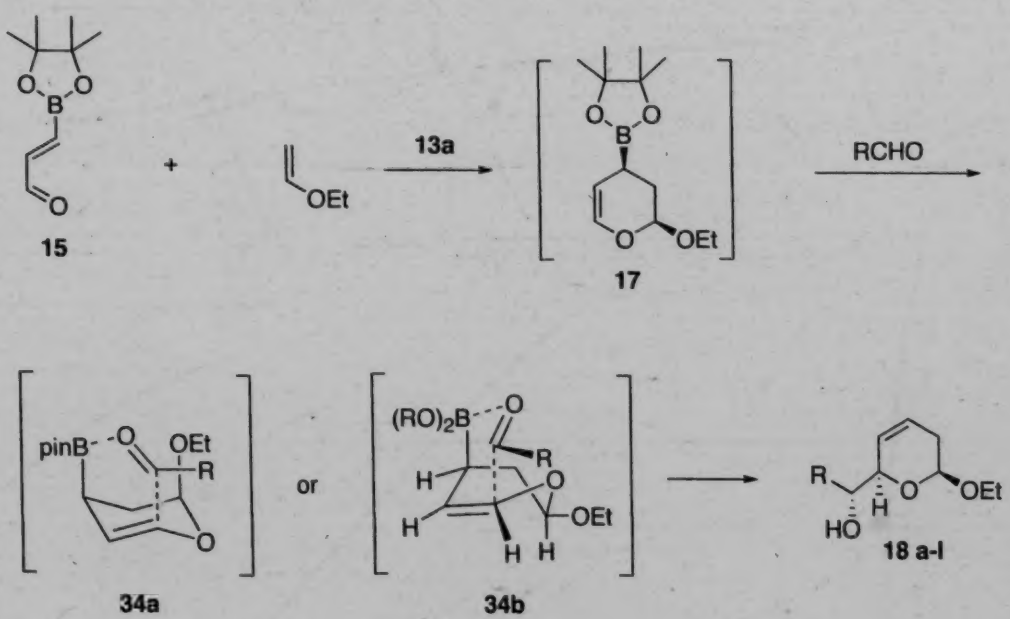


15 17 18

entry	aldehyde (R)	temp (°C)	time (h)	product[b]	yield[c] (%)
1	C_6H_5	40	24	**18a**	82
2	4-NO_2-C_6H_4	25	24	**18b**	92
3	4-MeO-C_6H_4	45	24	**18c**	81
4	$(CH_3)_2CHCH_2$	45	24	**18d**	81
5[d]	$(CH_3)_2CH$	50	18	**18e**	78
6	$TBSOCH_2$	45	24	**18f**	82
7	$C_{10}H_{21}$	45	24	**18g**	89
8[d]	CH_2=CH	25	24	**18h**	73
9[e]	(*E*)-4-NO_2-C_6H_4CH=CH	40	24	**18i**	81
10[e]	(*E*)-$CH_3CH(CH_3)$=C	60	48	**18j**	61
11[d]	(*E*)-$CH_3CH(CH_3)$=C	50	48	**18j**	76
12[d]	(*E*)-$EtCO_2CH(CH_3)$=C	25	24	**18k**	88
13[d]	$CH_3(CH_2)_4C\equiv C$	40	18	**18l**	86

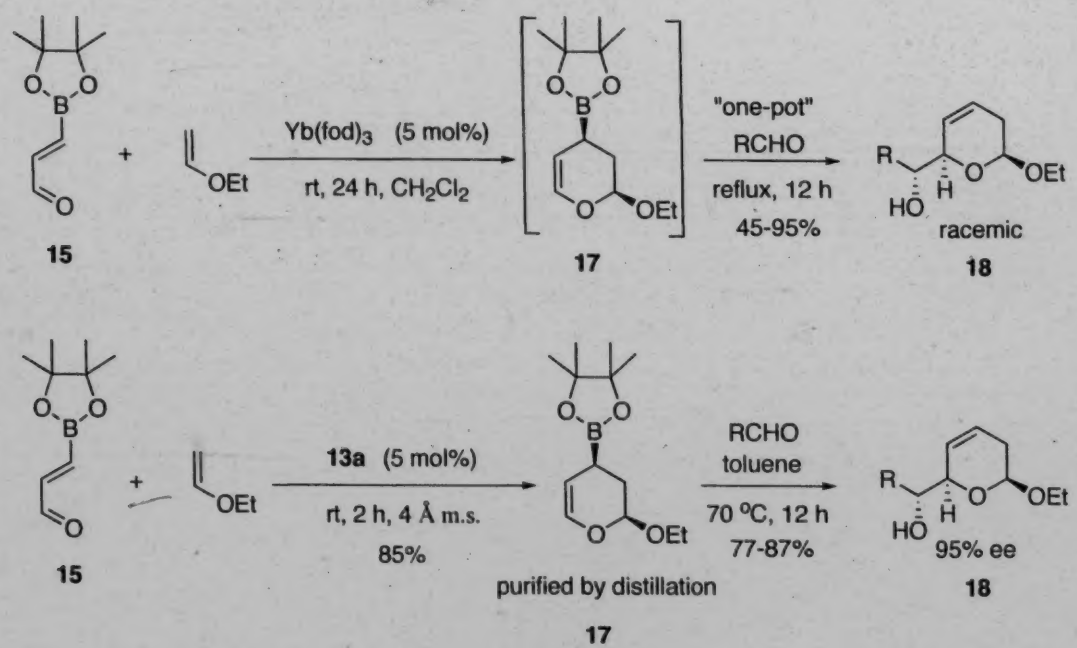
[a] Conditions: 2 mmol (0.36 g) of distilled, 1M in ethyl vinyl ether, with 1 mol% catalyst, 23°C, 1.5 h, followed by the addition of 2.0 equiv of aldehyde and reaction at the indicated temperature and time. [b] Diastereomerically pure. The absolute configuration of products **18g** was confirmed by total synthesis (see Chapter 4), the absolute configuration of all other products was assigned by analogy. [c] Yield of isolated, analytically pure product. [d] Ethyl vinyl ether was evaporated after step i, the step ii was carried out without solvent. [e] Ethyl vinyl ether was evaporated after step i, then step ii was carried out in dichloromethane (~1M).

The relative stereochemistry of the α-hydroxyalkyl dihydropyran products was first confirmed by X-ray crystallographic analysis.[19] The absolute stereochemistry of the optically enriched α-hydroxyalkyl dihydropyran products was confirmed by total synthesis of a natural product and by X-ray crystallographic analysis (see Chapter 4).[17,20] Mechanistically, the [4+2] cycloaddition of 1-boronoacrolein pinacolate (**15**) with ethyl vinyl ether is expected to proceed with complete *endo* selectivity to give the allylboronate intermediate. In the putative chair-like allylboration transition state **34** leading to **18**, the dihydropyran ring may assume an unfavorable chair-like conformation (i. e. **34a**) with both pseudo-axial boronate and ethoxy substituents. Alternately, a stereoelectronically viable boat-like conformation of type **34b** featuring a pseudo-equatorial ethoxy substituent may also be proposed (Scheme 3.10).[12]



Scheme 3.10

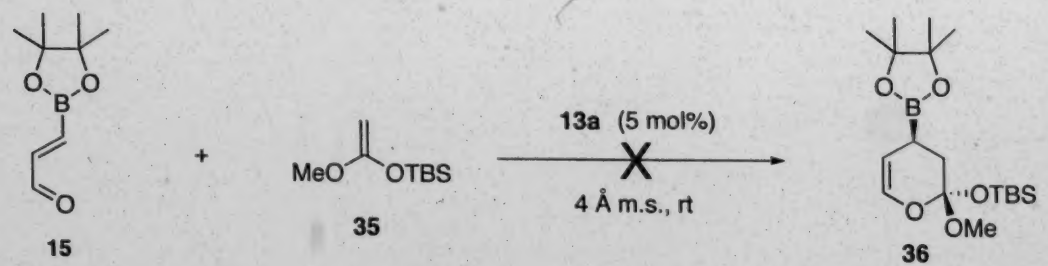
Coincidentally, Carboni and co-workers also recognized the potential of this methodology (Scheme 3.11). During the course of our study, they published the racemic version of the methodology using $Yb(fod)_3$ as a catalyst and dichloromethane as the solvent.[19] Furthermore, they reported the enantioselective version of the methodology using Jacobsen's Cr(III) catalyst shortly after we reported our own results.[20] However, in their reported procedure employing 5 mol% of **13a**, the cycloadduct **17** had to be purified by distillation to remove the catalyst before being subjected to the second allylboration step. As a result, the tandem process could not be performed in "one-pot" as achieved in our procedure. This methodology has been applied to a concise synthesis of (+)-Goniodiol,[21] which shows significant cytotoxity.



Scheme 3.11

3.4 Inverse electron demand hetero-Diels-Alder cycloaddition/allylboration using other dienophiles.

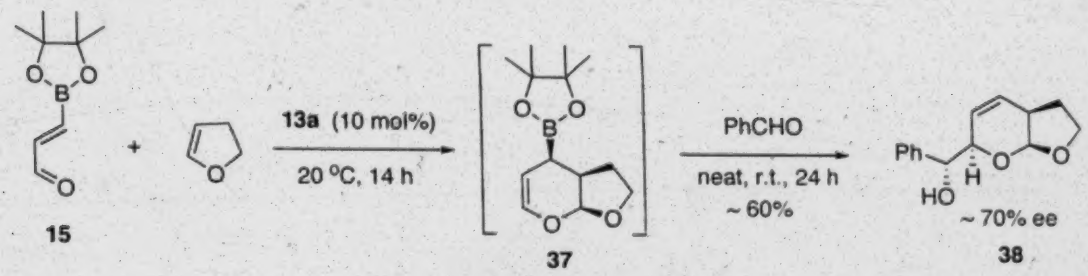
In addition to ethyl vinyl ether, a few other dienophiles were tested as well. We tried dienophile **35,** which was expected to react faster because of the presence of two ether donating groups in the structure. Disappointingly, no cycloaddition was observed under our standard conditions (Equation 3-5). The failure of this reaction could be explained by the significant increase in the steric bulk in **35** relative to that in ethyl vinyl ether.



Equation 3-5

2,3-Dihydrofuran was found to be an effective dienophile in the inverse electron demand Diels-Alder reaction with α,β-unsaturated acyl phosphonates and keto esters. Successful use of this dienophile in our three-component methodology would generate more complex dihydropyran derivatives with a carbon chain substituent at the C-2 position. As it turned out, we were glad to observe the formation of the cycloadduct **37** with 10% catalyst **13a** (Scheme 3.12). The resulting cycloadduct successfully underwent the allylboration step with benzaldehyde under solvent-free conditions to provide the final allylboration product **38**. Disappointingly, the product **38** was only obtained with

moderate enantioselectivity. The relative stereochemistry of the product **38** was determined by X-ray crystallographic analysis.



15 **37** **38**

Scheme 3.12

3.5 Conclusion

In summary, we have developed the first catalytic enantioselective hetero-Diels-Alder cycloaddition/allylboration reaction using ethyl vinyl ether as dienophile. 3-Boronoacrolein pinacolate (**15**) was found to be an exceptionally reactive hetero diene in this inverse electron demand hetero-Diels-Alder reaction. As a result, the reaction could be carried out with a very low catalyst loading. To explain the exceptional reactivity of aldehyde **15** as a hetero diene, a [5+2] transition state which involves a three-center two-electron system reminiscent of Singleton's vinylborane cycloadditions is proposed. In the allylboration step, a broad scope of aldehydes were tolerated and different reaction conditions were developed for different aldehydes in order to consistently obtain high yields. Overall, from the key intermediate **15**, this "one-pot" three-component reaction provides α-hydroxyalkyl dihydropyrans in good to excellent yields and with very high enantio- and diastereoselectivity.

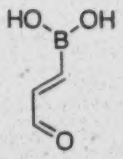
3.6 Experimental

3.6.1 General

The methods described in Section 2.7.1 also apply here with the following additions. Catalyst **13a** was prepared according to the procedure of Jacobsen.[6] Boronate **15** was prepared according to our previously published procedure and purified by bulb-to-bulb (<1 mm Hg, 94%).[3b] BaO (Acros) was used as supplied (90% tech powder). Powdered 4 Å molecular sieves (< 5 micron, Aldrich) were dried in a vacuum oven (138 °C) prior to use. Optical rotations were measured using a 1 mL cell with a 1 dm length on a P.E. 241 polarimeter.

3.6.2 Experimental procedures

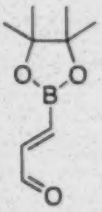
(*E*)-3-Boronoacrolein (28)



(*R*)-(+)-α-Pinene (91% ee, 10.8 mL, 66.7 mmol) was slowly added to a solution of borane-dimethyl sulfide complex (3.30 mL, 33.0 mmol) in THF (10 mL) at 0 °C under nitrogen. The solution was stirred for 10 minutes at 0 °C followed by 2 hours at room temperature. The resulting thick white suspension was cooled to 0 °C and propiolaldehyde diethyl acetal (4.50 mL, 31.0 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 hour and further stirred at room temperature for an additional hour, and cooled back again to 0 °C prior to the quick addition of freshly distilled

acetaldehyde (20.0 mL). The mixture was stirred for 30 minutes at 0 °C, then refluxed for 16 hours at 45 °C, then water (12 mL) was added at 0 °C. After 3 hours, the solution was transferred to a separatory funnel. The aqueous layer was extracted with ether (2 × 50 mL) and ethyl acetate (2 × 50 mL). The organic layers were combined and concentrated under reduced pressure. The resulting suspension was then triturated in cold hexanes and filtered to yield the boronic acid as a white solid. A second crop could be obtained by concentration of the filtrate and trituration in cold hexanes. If the product was still coloured, it could be washed with cold dichloromethane (2.50 g, 76%). IR (film cast) 3175, 2850, 1673 cm^{-1}; ^1H NMR (400 MHz, CD_3OD + 5% D_2O) δ 9.52 (d, J = 7.5 Hz, 1H), 6.80 (d, J = 18.0 Hz, 1H), 6.64 (dd, J = 18.0, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD + 5% D_2O) δ 197.6, 145.6, 105.1; HRMS (EI, *m/z*) calcd for $C_3H_5O_3B$ 100.0332, found 100.0334.

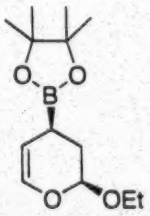
(*E*)-3-Boronoacrolein pinacol ester (15)



3-Borono-acrolein (**28**) (200 mg, 2.00 mmol) was dissolved in THF (15 mL) at room temperature, and pinacol (236 mg, 2.00 mmol) was added. The solution was stirred for 30 minutes then the solvent was evaporated under reduced pressure at 45 °C to afford a colorless oil. Addition of THF followed by concentration may be necessary to complete the condensation by azeotropic removal of the water. The crude oil was then purified by bulb-to-bulb distillation (1 mm Hg, 100 °C) to provide aldehyde **15** (343 mg, 94%). ^1H

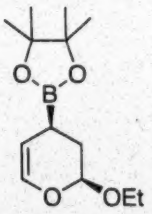
NMR (400 MHz, $CDCl_3$) δ 9.59 (d, J = 7.5 Hz, 1H), 6.78 (dd, J = 7.5, 18.1 Hz, 1H), 6.62 (d, J = 18.1 Hz, 1H), 1.28 (s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1, 147.1, 141.5, 84.5, 24.8.

(2*S*,4*S*)-2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-*2H*-pyran (17) (method A)



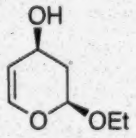
A mixture of 3-boronoacrolein pinacolate **15** (364 mg, 2.00 mmol) and ethyl vinyl ether (1.90 mL, 20.0 mmol) was placed in an oven dried 10 mL rbf with a stirbar. To this solution was added **13a** (9.60 mg, 0.020 mmol) and powdered 4Å molecular sieves (300 mg). The reaction was stirred for 14 hours at ambient temperature then filtered through celite and concentrated *in vacuo* to give crude **17.** ^1H NMR (500 MHz, $CDCl_3$) δ 6.22 (dd, J = 6.2, 2.1 Hz, 1H), 4.98 (dd, J = 3.8, 2.9 Hz, 1H), 4.82 (dd, J = 6.2, 4.4 Hz 1H), 3.82 (dq, J = 9.7, 7.1 Hz, 1H), 3.56 (dq, J = 9.7, 7.1 Hz, 1H), 1.96-2.02 (m, 2H), 1.73-1.79 (m, 1H), 1.16-1.23 (m, 15H).

(2*S*,4*S*)-2-Ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-*2H*-pyran (17) (method B)



A mixture of 3-boronoacrolein pinacolate **15** (364 mg, 2.00 mmol) and ethyl vinyl ether (1.90 mL, 20.0 mmol) was placed in an oven-dried 10 mL rbf with a stirbar. To this solution was added **13a** (2.90 mg, 0.006 mmol) and powdered BaO (200 mg). The reaction was stirred for 14 hours at ambient temperature, then filtered through celite and concentrated *in vacuo* to give crude **17**.

(2*S*,4*S*)-2-Ethoxy-4-hydroxy-3,4-dihydro-2*H*-pyran (29)

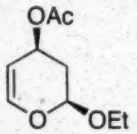


The Diels-Alder cycloadduct **17** was dissolved in THF (10 mL) and cooled to 0 °C. A 3M aqueous solution of NaOAc (1.00 mL, 3.00 mmol) was added dropwise and the temperature maintained below 5 °C. Hydrogen peroxide (0.610 mL, 6.55 mmol) was added and the mixture was stirred at 0 °C for 1 hour. Water (10 mL) was then added and the aqueous layer extracted with ether (2 × 30 mL). The ether layers were combined, washed with an aqueous saturated solutions of NH_4Cl (15 mL) and NaCl (15.0 mL), then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave the crude product **29**, which was purified by flash column chromatography (deactivated silica gel, pentane/ether 4:1) to provide **29** (234 mg, 81%) as a clear oil. $[\alpha]^{23}_D$ +136.0 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3553, 3431, 1646, 1297; ^1H NMR (500 MHz, $CDCl_3$) δ

6.24 (d, J = 6.2 Hz, 1H), 5.22 (dd, J = 2.2, 2.2 Hz, 1H), 5.13-5.17 (m, 1H), 3.90- 3.95 (m, 1H), 3.80 (dq, J = 9.7, 7.1 Hz, 1H), 3.52 (dq, J = 9.7, 7.1 Hz, 1H), 3.04 (d, J = 11.2 Hz, 1H), 2.21-2.25 (m, 1H), 2.02 (ddd, J = 14.5, 5.0, 2.7 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 105.9, 96.6, 64.2, 58.6, 35.0, 15.2; HRMS (EI, *m/z*) calcd for $C_7H_{12}O_3$ 144.07864, found 144.07827.

Assay of enantiomeric excess: Chiral HPLC analysis (Chiralpak AD-RH, 50% isopropanol/water, 0.300 mL/min, 210.8 nm), t_R(major)=8.60 min., t_R(minor)=10.64 min.) 96% ee.

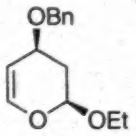
(2*S*,4*S*)-2-Ethoxy-4-acetoxy-3,4-dihydro-*2H*-pyran (32)



To a 25 mL rbf was added **29** (186 mg, 1.29 mmol), 2,6-lutidine (0.200 mL, 1.96 mmol) and DMAP (15.7 mg, 0.129 mmol) in dry CH_2Cl_2 (4 mL). The mixture was cooled to 0 °C and acetic anhydride was added via syringe (0.120 mL, 1.29 mmol). The reaction mixture was stirred at 0 °C for 1 hour and further stirred at ambient temperature overnight. Water (10 mL) and ether (30 mL) was added to the solution. The phases were separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with an aqueous saturated solution of NaCl, dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash column chromatography (deactivated silica-gel, hexanes/ether 9:1) to provide **32** (233 mg, 96%) as a colorless oil. $[\alpha]^{23}_D$ +37.0 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3071, 2929, 1730, 1650, 1244; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (dd, J = 6.3, 1.0 Hz, 1H), 5.26-5.32 (m, 1H), 5.06 (dd, J

= 5.2, 2.9 Hz, 1H), 4.96 (dd, *J* = 6.3, 4.9 Hz, 1H), 3.90 (dq, *J* = 9.7, 7.1 Hz, 1H), 3.58 (dq, *J* = 9.7, 7.1 Hz, 1H), 2.06-2.30 (m, 2H), 2.05 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 144.2, 100.7, 96.6, 64.5, 62.7, 33.0, 21.3, 15.0; HRMS (EI, *m/z*) calcd for $C_9H_{14}O_4$ 186.08920, found 186.08969.

(2*S*,4*S*)-2-Ethoxy-4-benzyloxy-3,4-dihydro-*2H*-pyran (33)



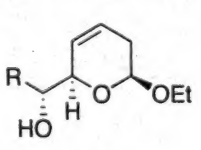
To a solution of **29** (570 mg, 3.95 mmol) in DMF (10 mL) cooled in an ice-water bath was added NaH (95%, 131 mg, 5.20 mmol). The mixture was stirred at 0 °C for 30 minutes. then benzyl bromide (0.570 mL, 4.80 mmol) was added dropwise. The reaction mixture was slowly warmed to ambient temperature and stirred overnight. The mixture was added to water (25 mL) and ether (50 mL) and the phases were separated. The aqueous layer was extracted with ether (2 × 30 mL), and the combined organic layers were washed with an aqueous saturated solution of NaCl, dried over anhydrous $MgSO_4$, concentrated and purified by flash column chromatography (deactivated silica-gel, hexanes/ether 95:5) to provide **33** (878 mg, 95%) as a colorless oil. $[\alpha]^{23}_D$ +22.8 (c=1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3064, 2976, 1646, 1229; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.20 (m, 5H), 6.30 (dd, *J* = 6.3, 1.3 Hz, 1H), 4.99 (dd, *J* = 7.7, 2.5 Hz, 1H), 4.92 (ddd, *J* = 6.3, 2.8, 1.0 Hz, 1H), 4.56 (d, *J* = 1.3Hz, 2H), 4.15-4.20 (m, 1H), 3.88 (dq, *J* = 9.7, 7.1 Hz, 1H), 3.58 (dq, *J* = 9.7, 7.1 Hz, 1H), 2.22 (dddd, *J* = 13.3, 6.4, 2.5, 1.1 Hz, 1H), 2.05 (ddd, *J* = 13.3, 7.5, 7.5 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 143.0, 138.6, 128.3, 127.6, 127.5, 102.8, 98.2, 69.7, 67.9, 64.5, 34.3, 15.1; HRMS (EI, *m/z*) Calcd for $C_{14}H_{18}O_3$ 234.12560, found 234.12579.

General procedure for the preparation of 18a-d, 18f and 18g

A mixture of 3-boronoacrolein pinacolate **15** (364 mg, 2.00 mmol) and ethyl vinyl ether (1.90 mL, 20.0 mmol) was placed in an oven dried 10 mL rbf with a stirbar. To this solution was added **13a** (9.60 mg, 0.020 mmol) and powdered BaO (400 mg). After stirring for 1.5 hour at ambient temperature (23 °C), aldehyde (4.00 mmol) was added to the reaction mixture. The reaction mixture was stirred at 40 or 45 °C for 24 hours, then diluted with ethyl acetate and filtered through celite. The ethyl acetate solution was then stirred for 30 minutes with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with an aqueous saturated solution of NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford title compound as a crude product. Purification by flash column chromatography (deactivated silica gel, hexanes/ether) led to the pure title compound.

(1*R*)-((2*S*, 6*R*)-6-Ethoxy-5, 6-dihydro-2*H*-pyran-2-yl)-phenyl-methanol (18a)

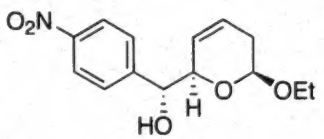


Colorless oil, yield (384 mg, 82%). $[\alpha]^{23}_D$ +24.9 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}): 3451, 3035, 2877, 1640, 1257; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.40 (m,

5H), 5.75-5.79 (m, 1H), 5.36-5.40 (m, 1H), 4.78 (dd, J = 5.9, 5.9 Hz, 1H), 4.56 (dd, J = 7.4, 1.5 Hz, 1H), 4.28-4.32 (m, 1H), 3.96 (dq, J = 9.7, 7.1 Hz, 1H), 3.58 (dq, J = 9.7, 7.1 Hz, 1H), 3.11 (brs, 1H), 2.10-2.12 (m, 2H), 1.25 (t, J = 7.1Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 128.3, 128.0, 127.2, 125.4, 124.8, 98.5, 78.7, 76.8, 64.5, 31.1, 15.3; HRMS (ESI, *m/z*) calcd for $C_{14}H_{18}O_3Na$ 257.115364, found 257.115200.

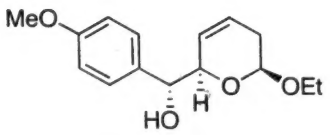
Assay of enantiomeric excess: Chiral HPLC analysis (chiralpak AD-RH, 50% isopropanol/water, 0.300 mL/min, 210.8 nm), t_R(major)=8.60 min., t_R(minor)=10.64 min.) 96% ee

(1*R*)-((2*S*,6*R*)-6-Ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-(4-nitro-phenyl)-methanol (18b)



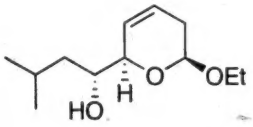
Brown solid. yield (510 mg, 92%). Mp 102-103 °C; $[\alpha]^{23}_D$ +23.0 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3442, 2977, 1604, 1519, 1431; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 5.82-5.88 (m, 1H), 5.46-5.50 (m, 1H), 4.79 (dd, J = 6.3, 3.9 Hz, 1H), 4.75 (dd, J = 4.9, 4.9 Hz, 1H), 4.35-4.39 (m, 1H), 3.83 (dq, J = 9.6, 7.1 Hz, 1H), 3.52 (dq, J = 9.6, 7.1 Hz, 1H), 3.39 (d, J = 3.9 Hz, 1H), 2.18-2.25 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 147.5, 127.8, 125.6, 124.7, 123.4, 98.1, 77.8, 75.6, 64.7, 30.8, 15.3; HRMS (EI, *m/z*) calcd for $C_{14}H_{16}O_5N$ 278.10284, found 278.10265.

(1*R*)-((2*S*,6*R*)-6-Ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-(4-methoxy-phenyl)-methanol (18c)



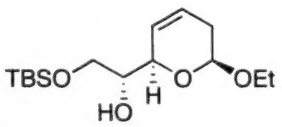
Colorless oil, yield (428 mg, 81%). $[\alpha]^{23}_{D}$ +24.3 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3442, 2977, 1604, 1519, 1431; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 5.72-5.78 (m, 1H), 5.32-5.36 (m, 1H), 4.79 (dd, *J* = 7.7, 5.3Hz, 1H), 4.50 (d, *J* = 7.7 Hz, 1H), 4.26-4.30 (m, 1H), 4.01 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.80 (s, 3H), 3.59 (dq, *J* = 9.6, 7.1Hz, 1H), 3.18 (brs, 1H), 2.19-2.23 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 131.9, 128.5, 125.4, 124.7, 113.7, 98.5, 78.8, 76.4, 64.5, 55.2, 31.1, 15.2; HRMS (EI, *m/z*) calcd for $C_{15}H_{20}O_4$ 264.13617, found 264.13670.

(1*R*)-((2*S*,6*R*)-6-Ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-3-methyl-butan-1-ol (18d)



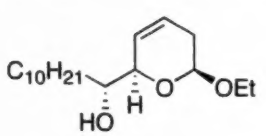
Colorless oil, yield (347 mg, 81%). $[\alpha]^{23}_{D}$ +98.0 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3446, 3041, 1467, 1293; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79-6.05 (m, 1H), 5.62-5.68 (m, 1H), 4.73 (dd, *J* = 5.5, 5.5 Hz, 1H), 4.07-4.11 (m, 1H), 3.96 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.50-3.66 (m, 2H), 2.42 (d, *J* = 5.7 Hz, 1H), 2.18-2.23 (m, 2H), 1.80-1.90 (m, 1H), 1.50-1.60 (m, 1H), 1.22-1.38 (m, 4H), 0.96 (d, *J* = 7.8Hz, 3H), 0.93 (d, *J* = 7.8Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 126.6, 124.7, 98.4, 77.7, 71.4, 64.2, 41.9, 31.1, 24.4, 23.6, 21.8, 15.1; HRMS (ESI, *m/z*) calcd for $C_{12}H_{22}O_3Na$ 237.14612, found 237.14607.

2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-((2*S*,6*R*)-6-ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-ethanol (18f)



Colorless oil, yield (496 mg, 82%). $[\alpha]^{23}_{D}$ +34.5 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3324, 3038, 2857, 1317; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78-5.86 (m, 1H), 5.66-5.70 (m, 1H), 4.76 (dd, *J* = 6.2, 4.7 Hz, 1H), 4.41-4.45 (m, 1H), 3.93 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.60-3.76 (m, 3H), 3.50 (dq, *J* = 9.6, 7.1 Hz, 1H), 2.62 (d, *J* = 5.9 Hz, 1H), 2.18-2.22 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 126.8, 124.5, 98.4, 73.9, 73.2, 64.4, 63.2, 31.0, 25.9, 18.2, 15.1, -5.4, -5.5; HRMS (ESI, *m/z*) calcd for $C_{15}H_{30}O_4NaSi$ 325.18056, found 325.18041.

(1*R*)-((2*S*,6*R*)-6-Ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-undecan-1-ol (18g)

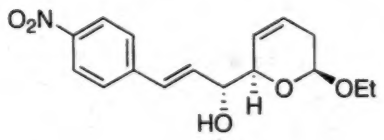


Colorless oil, yield (530 mg, 89%). $[\alpha]^{23}_{D}$ +54.7 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3454, 3040, 2854, 1209; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80-5.86 (m, 1H), 5.62-5.68 (m, 1H), 4.76 (dd, *J* = 5.5, 5.5 Hz, 1H), 4.12-4.16 (m, 1H), 3.96 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.46-3.62 (m, 2H), 2.42 (d, *J* = 5.7 Hz, 1H), 2.19-2.23 (m, 2H), 1.20-1.60 (m, 21H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 126.7, 124.7, 98.5, 77.2, 73.3, 64.3, 33.0, 31.9, 31.1 29.7, 29.6, 29.6, 29.5, 29.3, 25.6, 22.6, 15.1, 14.0; HRMS (EI, *m/z*) calcd for $C_{18}H_{34}O_3$ 298.25079, found 298.25044.

General procedure for the preparation of 18i and 18j

A mixture of 3-boronoacrolein pinacolate (**15**) (364 mg, 2.00 mmol) and ethyl vinyl ether (1.90 mL, 20.0 mmol) was placed in an oven dried 10 mL rbf with a stirbar. To this solution was added **13a** (9.60 mg, 0.020 mmol) and BaO (400 mg). After 1.5 hour of stirring at ambient temperature (23 °C), the ethyl vinyl ether was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (1 mL) and the aldehyde (4.00 mmol) was added to the solution. The reaction was stirred at 40 or 60 °C for 24 hours to 48 hours, then diluted with ethyl acetate and filtered through celite. The ethyl acetate solution was stirred for 30 minutes with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with an aqueous saturated solution of NaCl then dried over anhydrous $MgSO_4$, filtered, and concentrated to afford title compound as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexanes/ether) led to the pure title compound.

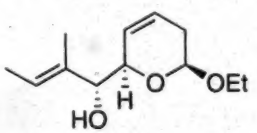
(1*R*)-((2*S*,6*R*)-6-Ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-3-(4-nitro-phenyl)-2-prop-2*E*-en-1-ol (18i)



Brown solid, yield (495 mg, 81%). Mp 99-100 °C; $[\alpha]^{23}_D$ +55.0 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3426, 1650, 1596, 1432, 1210; ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 16.0 Hz, 1H), 6.45 (dd, *J* =

16.0, 5.2 Hz, 1H), 5.83-5.88 (m, 1H), 5.66-5.71 (m, 1H), 4.80 (dd, *J* = 6.4, 3.8 Hz, 1H), 4.25-4.32 (m, 2H), 3.95 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.57 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.02 (br s, 1H), 2.15-2.35 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9, 143.1, 133.2, 129.9, 127.0, 125.2, 125.2, 123.9, 98.1, 77.1, 74.3, 64.7, 30.9, 15.2; HRMS (ESI, *m/z*) calcd for $C_{16}H_{19}O_5NNa$ 328.116093, found 328.116463.

(1*R*)-((2*S*,6*R*)-6-Ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-2-methyl-but-2*E*-en-1-ol (18j)



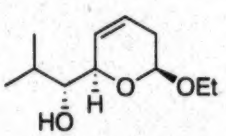
Colorless oil, yield (261 mg, 61%). $[\alpha]^{23}_D$ +57.1 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3462, 3041, 1650, 1256; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76-5.82 (m, 1H), 5.46-5.62 (m, 2H), 4.78 (dd, *J* = 6.2, 5.0 Hz, 1H), 4.22-4.28 (m, 1H), 3.86-4.02 (m, 2H), 3.58 (dq, *J* = 9.6, 7.1 Hz, 1H), 2.80 (brs, 1H), 2.19-2.23 (m, 2H), 1.62-1.66 (m, 6H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.8, 126.0, 124.4, 124.2, 98.6, 79.9, 76.0, 63.4, 31.1, 15.2, 13.1, 11.6; HRMS (ESI, *m/z*) calcd for $C_{12}H_{20}O_3Na$, 235.13047, found 235.12994.

Solvent-free procedure for the preparation of 18e, 18h, and 18j-l

A mixture of 3-boronoacrolein pinacolate (**15**) (364 mg, 2.00 mmol) and ethyl vinyl ether (1.9 mL, 20.0 mmol) was placed in an oven dried 10 mL rbf with a stirbar. To this solution was added **13a** (9.60 mg, 0.020 mmol) and BaO (400 mg). After 1.5 hour of stirring at ambient temperature (23 °C), the ethyl vinyl ether was evaporated *in vacuo* and the aldehyde (4.00 mmol) was added to the residue. The reaction was stirred at ambient

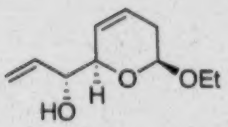
or elevated temperature for 18-48 hours, then diluted with ethyl acetate and filtered through celite. The ethyl acetate solution was stirred for 30 minutes with an aqueous saturated solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with an aqueous saturated solution of NaCl then dried over anhydrous $MgSO_4$, filtered, and concentrated to afford title compound as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexanes/ether) led to the pure title compound.

(1*R*)-((2*S*,6*R*)-6-Ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-3-methyl-prop-1-ol (18e)



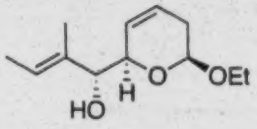
Colorless oil, yield (270 mg, 78%). $[\alpha]^{23}_{D}$ -71.0 (c = 1.6, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3454, 3039, 1471, 1237; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79-5.86 (m, 1H), 5.61-5.66 (m, 1H), 4.75 (dd, *J* = 6.0, 5.0 Hz, 1H), 4.32-4.37 (m, 1H), 3.96 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.58 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.21 (ddd, *J* = 7.0, 7.0, 3.9 Hz), 2.32 (d, *J* = 7.2 Hz, 1H), 2.19-2.25 (m, 2H), 1.91 (octet, *J* = 6.8 Hz, 1H), 1.62-1.66 (m, 6H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.4, 124.6, 98.4, 78.1, 75.0, 64.3, 30.9, 30.6, 19.5, 18.1, 15.1; HRMS (ESI, *m/z*) calcd for $C_{11}H_{20}O_3Na$ 223.13047, found 223.13032.

(1*R*)-((2*S*,6*R*)-6-Ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-2-prop-2-en-1-ol (18h)



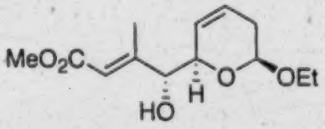
Colorless oil, yield (73%). $[\alpha]^{23}_{D}$ +101.95 (c = 5.2, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3448, 3042, 1648, 1210; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80-5.98 (m, 2H), 5.63-5.69 (m, 1H), 5.40 (ddd, *J* = 16.3, 1.7, 1.7 Hz, 1H), 5.27 (ddd, *J* = 10.4, 1.7, 1.7 Hz, 1H), 4.78 (dd, *J* = 6.3, 4.3 Hz, 1H), 4.15-4.21 (m, 1H), 4.05 (dd, *J* = 6.2, 6.2 Hz, 1H), 4.02 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.58 (dq, *J* = 9.6, 7.1 Hz, 1H), 2.82 (brs, 1H), 2.20-2.30 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 125.7, 124.7, 117.3, 98.2, 77.1, 74.9, 64.4, 30.9, 15.1; HRMS (ESI, *m/z*) calcd for $C_{10}H_{16}O_3Na$ 207.09917, found 207.09903.

(1*R*)-((2*S*,6*R*)-6-Ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-2-methyl-but-2*E*-en-1-ol (18j)



Colorless oil, yield (323 mg, 76%). Physical properties as described before.

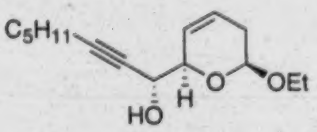
(4*R*)-((2*S*,6*R*)-6-Ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-4-hydroxy-3-methyl-but-2*E*-enoyl-oxy-ethane (18k)



Colorless oil, yield (476 mg, 88%). $[\alpha]^{23}_{D}$ -53.3 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3464, 2977, 1714, 1652; ^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.82-5.88 (m, 1H), 5.58-5.62 (m, 1H), 4.73-4.77 (m, 1H), 4.41-4.45 (m, 1H), 4.15 (q, *J* = 7.1

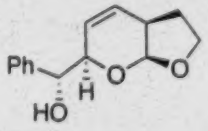
Hz, 2H), 3.97-4.01 (m, 1H), 3.86 (dq, J = 9.6, 7.1 Hz, 1H), 3.52 (dq, J = 9.6, 7.1 Hz, 1H), 3.12 (d, J = 6.3 Hz, 1H), 2.19-2.26 (m, 2H), 2.18 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 156.7, 125.8, 124.8, 117.1, 97.7, 77.8, 74.9, 64.4, 59.5, 30.4, 15.2, 15.0, 14.2; HRMS (ESI, *m/z*) calcd for $C_{14}H_{22}O_5Na$ 293.13594, found 293.113590.

(1*R*)-((2*S*,6*R*)-6-Ethoxy-5,6-dihydro-2*H*-pyran-2-yl)-2-octyn-1-ol (18l)



Colorless oil, yield (86%). $[\alpha]^{23}_D$ 87.16 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3441, 3043, 1652, 1210; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78-5.95 (m, 2H), 4.82 (dd, J = 6.4, 4.0 Hz, 1H), 4.22-4.32 (m, 1H), 4.02 (dq, J = 9.6, 7.1 Hz, 1H), 3.58 (dq, J = 9.6, 7.1 Hz, 1H), 2.92 (d, J = 4.0 Hz, 1H), 2.19-2.26 (m, 4H), 1.50-1.58 (m, 2H), 1.30-1.40 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.5, 124.8, 98.1, 87.0, 77.6, 77.4, 65.4, 64.5, 31.0, 30.8, 28.2, 22.1, 18.7, 15.1, 13.9; HRMS (ESI, *m/z*) calcd for $C_{15}H_{24}O_3Na$ 275.16177, found 275.16186.

6-α-Hydroxybenzyl-2,3,3α,7α-tetrahydro-6-H-furo[2,3-β]pyran (38)



A mixture of 3-boronoacrolein pinacolate (**15**) (182 mg, 1.00 mmol) and 2,3-dihydrofuran (700 mg, 10.0 mmol) was placed in an oven dried 10 mL rbf with a stirbar. To this solution was added **13a** (48.0 mg, 0.100 mmol) and BaO (400 mg). After 1.5

hours of stirring at ambient temperature (23 °C), the ethyl vinyl ether was evaporated *in vacuo* and benzaldehyde (212 mg, 2.00 mmol) was added to the residue. The reaction was allowed to stir at room temperature for 24 hours, then diluted with ethyl acetate and filtered through celite. The ethyl acetate solution was stirred for 30 minutes with an aqueous saturated solution of $NaHCO_3$ (2 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with an aqueous saturated solution of NaCl then dried over anhydrous $MgSO_4$, filtered, and concentrated to afford **38** as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexanes/ethyl acetate 4:1) led to the pure product **38** (141 mg, 61%) as an oil, which crystallized when stored at -5 °C. $[\alpha]^{23}_D$ -10.19 (c = 1.23, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 3435, 3046, 2877, 1257; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 10.2, 4.4, Hz, 2.3 1H), 5.56 (ddd, *J* = 10.2, 1.7, 1.7 Hz, 1H), 5.18 (d, *J* = 4.1 Hz, 1H), 4.61 (d, *J* = 7.5 Hz, 1H), 4.28-4.31 (m, 1H), 4.22 (ddd, *J* = 8.2, 8.2, 4.8 Hz, 1H), 3.96 (ddd, *J* = 7.7, 7.7, 7.5 Hz, 1H), 3.42 (brs, 1H), 2.52-2.60 (m, 1H), 2.15-2.22 (m, 1H), 1.73-1.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 128.3, 128.1, 127.3, 127.1, 125.8, 100.6, 77.2, 76.6, 68.2, 38.4, 30.4; HRMS (ESI, *m/z*) calcd for $C_{14}H_{16}O_3Na$ 255.09917, found 255.09926.

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Chapter 4

Catalytic Enantioselective Synthesis of (5*R*,6*S*)-6-Acetoxy-Hexadecanolide, a Mosquito Oviposition Attractant Pheromone

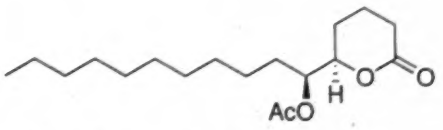
4.1 Introduction

The mosquito is one of the most important vectors for infectious viruses causing human or animal diseases. More than 100 mosquito-borne viruses have been identified to date. Amongst them, the West Nile Virus, which is now present all over the world, has imposed a great threat to human and animal health.

Initially isolated in Uganda, West Nile Virus is now documented to be the most widely distributed flavivirus and occurs in many parts of Africa, Asia and Europe. West Nile Virus arrived in New York state in 1999, and subsequently spread across the U.S. and most of the provinces of Canada in a few years. Although West Nile Virus sickens thousands of people and kills hundreds each year only in North America, it is primarily an avian disease. To date, the virus has been found in many species of birds and a significant number of birds have been found to be killed by the virus in recent years. If the spread of West Nile Virus in birds becomes out of control, some species may soon be extinct in a matter of years.[1]

One efficient way to prevent the spread of the West Nile Virus and other mosquito related diseases is to kill the vector mosquito by using mosquito traps. In some

types of traps, mosquito pheromones play an important role to draw and trap mosquitoes. These pheromones have received a significant amount of attention from the synthetic community. (5*R*,6*S*)-6-Acetoxy-hexadecanolide (Figure 4-1),[2] the major component of the oviposition attractant pheromone of *Culex* mosquito (the primary vector of West Nile Virus), is one of these key molecules. When they lay eggs, female *Culex* mosquitoes release this compound to attract other pregnant females to this site. Thus, this pheromone could be used in traps that will attract and kill ensnared insects.



(5*R*, 6*S*)-6-acetoxy-5-hexadecanolide (**1**)

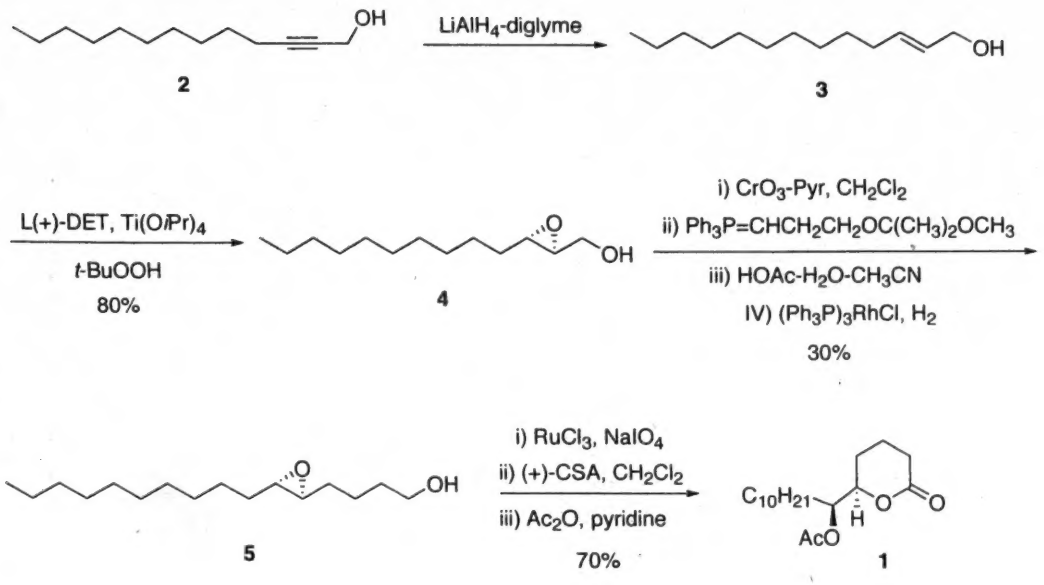
Figure 4-1. (5*R*,6*S*)-6-Acetoxy-hexadecanolide (**1**), the oviposition attractant pheromone of female *Culex* mosquito

4.2 Catalytic asymmetric routes to (5R,6S)-6-acetoxy-hexadecanolide by other groups.

Owing to its remarkable biological activity, a number of total syntheses of (5*R*, 6*S*)-6-acetoxy-hexadecanolide[3] have been published since its isolation. The major challenge in the synthesis is the enantioselective introduction of the chiral diol functionality. While some synthetic routes start with chiral material to establish the two chiral centers,[3a, 3b, 3e, 3f] the most elegant synthetic routes are based on catalytic asymmetric reactions.[3c, 3d, 3g, 3h, 3i] Amongst the few reliable and predictable ways to access chiral epoxides and diols, Sharpless asymmetric epoxidation[4] and dihydroxylation[5]

reactions have been extensively used in the syntheses of pheromone **1**. With the recent development catalytic asymmetric reactions promoted by proline and its derivatives,[6] unsurprisingly, this new methodology was applied in the synthesis of **1** as well. In this section, catalytic asymmetric routes to pheromone **1** will be briefly reviewed.

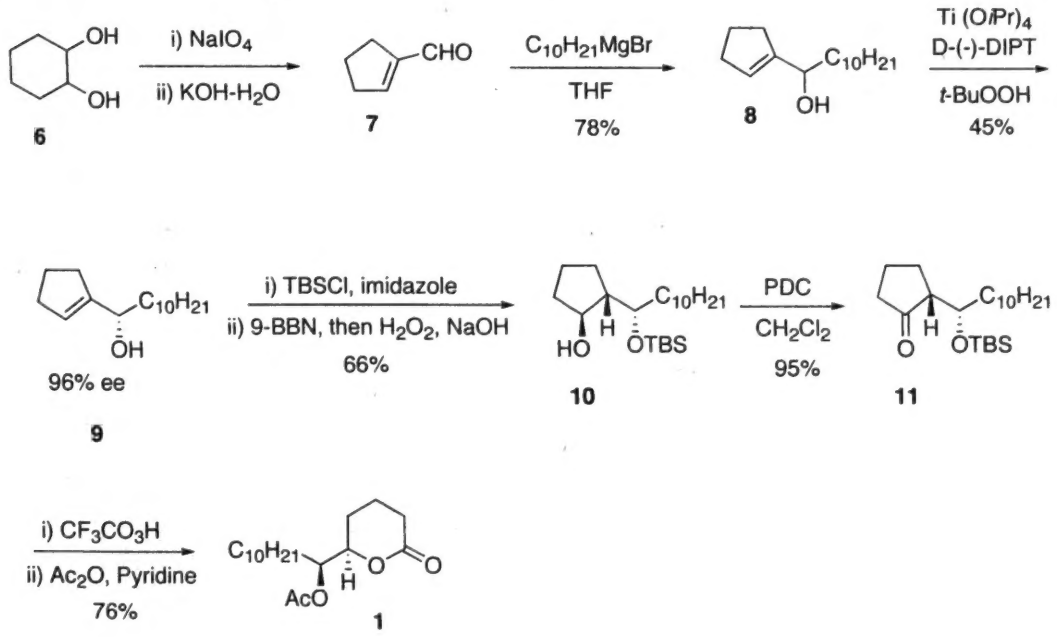
The first catalytic asymmetric synthesis of the pheromone was published by Professor Lin and co-workers (Scheme 4.1).[3c] This route involved a Sharpless asymmetric epoxidation (AE) as the key step to establish the two chiral centers in the molecule. Lin's synthesis commenced with reduction of the known propargylic alcohol **2** using $LiAlH_4$ to provide the corresponding *trans*-allylic alcohol **3**. Hydroxyl-directed epoxidation of the allylic alcohol under Sharpless AE conditions afforded the desired chiral epoxide **4** in 80% yield with 96% ee. Oxidation of the alcohol to the corresponding aldehyde with Collins reagent, followed by a Wittig reaction, deprotection of the 2-methoxy-2-propyl ether, and homogenous hydrogenation of the olefin gave intermediate **5**. Reaction of **5** with $RuCl_3$ and $NaIO_4$ provided the corresponding carboxylic acid, which was then transformed into the natural product via lactonization under acidic conditions followed by acetylation. In summary, using this route compound **1** was reached with an overall yield of 15-20% from known intermediate **2** in nine steps.



Scheme 4.1

Professor Zhou and co-workers[3d] completed the second catalytic asymmetric synthesis of **1** based on a kinetic resolution of racemic alcohol **8** using a Sharpless AE reaction (Scheme 4.2). The total synthesis began with a simple two-step conversion of a mixture of *trans*- and *cis*-1,2-cyclohexanediol **6** to aldehyde **7**. The aldehyde **7** was reacted with the Grignard reagent ($C_{10}H_{21}MgBr$) to give the racemic allylic alcohol **8**. The kinetic resolution of alcohol **8** was realized by treatment of **8** under Sharpless AE conditions to afford chiral alcohol **9** in 45% yield with 96% ee. Protection of the alcohol in **9** with a TBS group, hydroboration of the resulting intermediate followed by oxidation of the C-B bond with H_2O_2/NaOH gave compound **10**. The latter was then converted to ketone **11** by reaction with PDC. Removal of the TBS protecting group and Baeyer-Villiger oxidation of the cyclopentanone moiety to a lactone with CF_3CO_3H, followed by

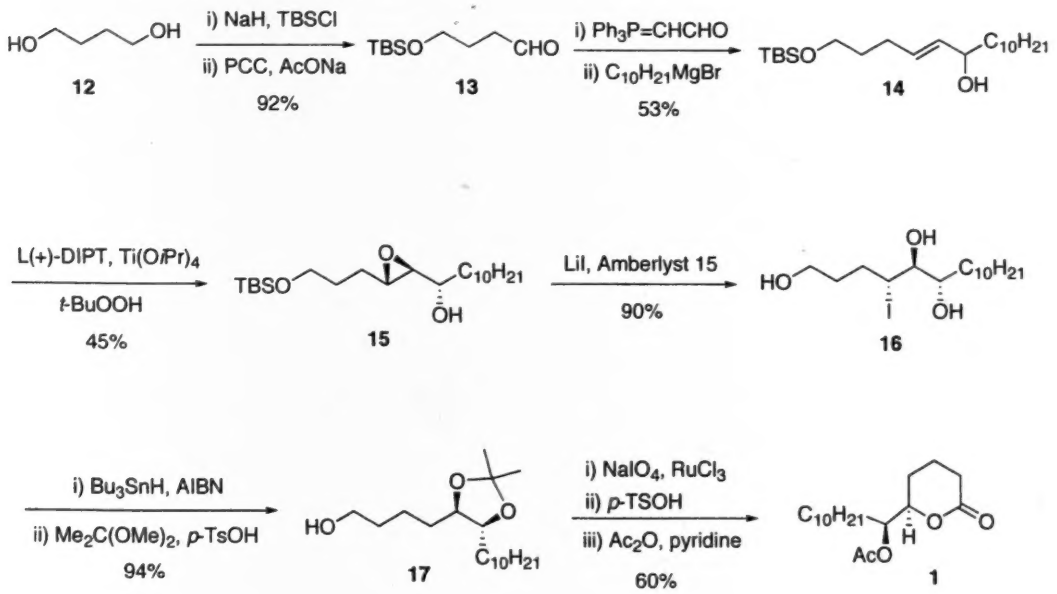
acetylation, completed the synthesis of **1**. Overall, this route requires nine steps in 17% yield from **7**.



Scheme 4.2

The third catalytic asymmetric synthesis of **1** was published by Professor Bonini and co-workers.[3g] Like Zhou and co-workers, Bonini and co-workers chose to employ a kinetic resolution of allylic alcohol **14** using a Sharpless AE reaction (Scheme 4.3). Monosilylation of 1,4-butanediol and oxidation of the unprotected hydroxyl group with PCC provided aldehyde **13**. Reaction of aldehyde **13** with formylmethylenetriphenylphosphorane gave the corresponding α,β-unsaturated aldehyde, which was further reacted with n-decylmagnesium bromide to afford racemic allylic alcohol **14**. Uneventfully, the allylic alcohol **14** was transformed into chiral epoxy alcohol **15** with 95% ee under Sharpless AE conditions. Regioselective opening of the epoxide

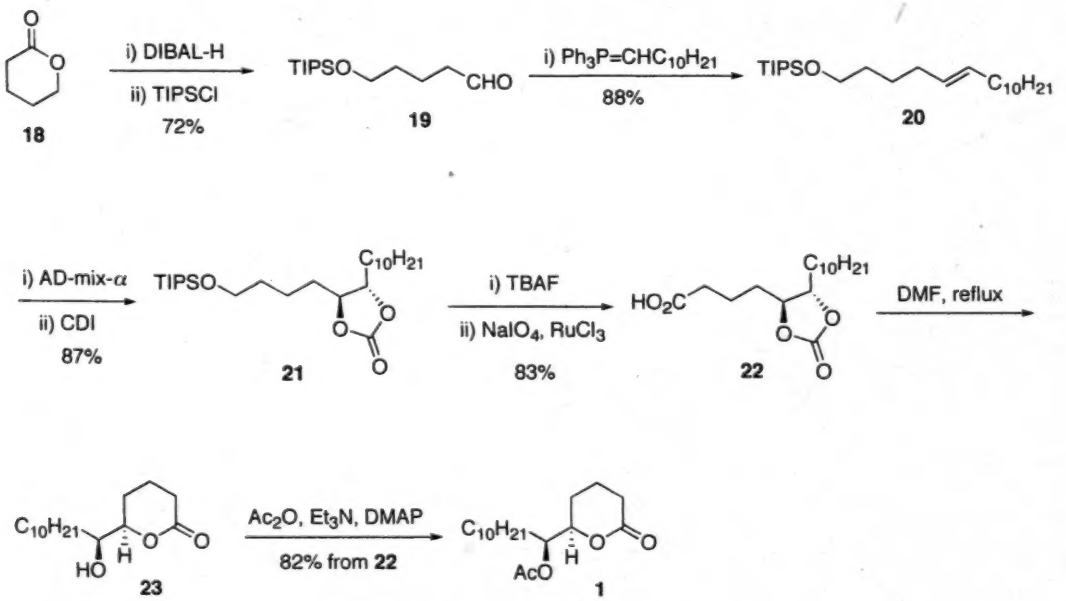
under acidic conditions and concomitant removal of the TBS protecting group provided **16**. Reduction of **16** with n-Bu_3SnH and AIBN afforded the corresponding diol, which was then protected as acetonide **17**. Finally, oxidation of the primary hydroxyl group to the carboxylic acid, deprotection of the diol followed by subsequent lactonization and acetylation gave the final lactone **1**. The total synthesis of **1** was thus completed in 11% overall yield from **12** in eleven steps.



Scheme 4.3

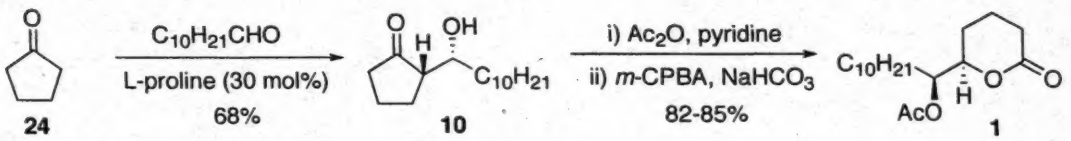
The fourth catalytic asymmetric synthesis of **1** was accomplished by Professor Couladouros and co-workers.[3h] In this work a Sharpless asymmetric dihydroxylation reaction was employed to set up the two chiral centers of **1** (Scheme 4.4). The total synthesis began with a simple two-step conversion of **18** to aldehyde **19**. The latter then underwent a Wittig reaction to provide compound **20**. A Sharpless asymmetric dihydroxylation and subsequent protection of the diol as a cyclic carbonate provided

intermediate **21**. Deprotection of the TIPS ether and oxidation of the resulting alcohol to the carboxylic acid gave compound **22**. Lactonization in refluxing DMF followed by acetylation afforded pheromone **1** after eight steps with a 36% overall yield.



Scheme 4.4

The most recent and shortest synthesis of **1**, published in 2005 by Professor Li and co-workers,[3i] employed an L-proline catalyzed asymmetric aldol reaction as the key step (Scheme 4.5). The synthesis commenced with the direct aldol reaction between cyclopentanone (**24**) and undecanal catalyzed by L-proline to provide intermediate **10** in 68% yield with 96% ee. Acetylation of **10** followed by Baeyer-Villiger oxidation led to the natural pheromone **1**. Impressively, the whole sequence only took three steps in 58% overall yield.



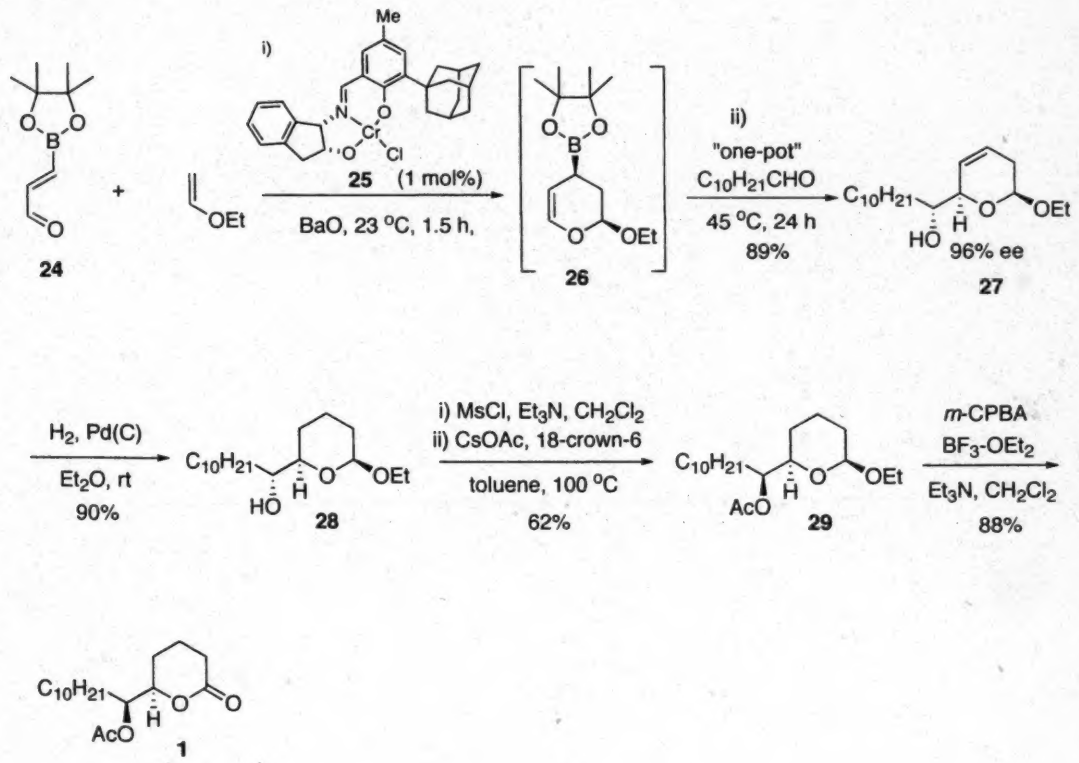
Scheme 4.5

4.3 Our approach to (5*R*,6*S*)-6-acetoxy-hexadecanolide and its C6 epimer.

As we described in Chapter 3, we developed an efficient way to construct α-hydroxyalkyl dihydropyrans via the three-component inverse electron demand hetero-Diels-Alder cycloaddition/allylboration reaction. These chiral pyran derivatives could serve as starting materials to access a variety of structural motifs such as δ–lactones. In response to the increasing demand for an efficient route to **1** and its analogs, we initiated a project to synthesize **1** and its C6 epimer. In addition, the absolute configuration of the α-hydroxyalkyl dihydropyrans was not known at that time. The total synthesis of **1** can also be used to determine the absolute stereochemistry of these dihydropyrans.

The synthesis began with a three-component hetero-Diels-Alder cycloaddition/allylboration reaction involving 3-boronoacrolein pinacolate **24**, ethyl vinyl ether and undecanal in the presence of 1 mol% of Jacobsen's Cr(III) chiral catalyst to provide dihydropyran **27**.[7] Gratifyingly, it was found that the reaction could be carried out in gram scale (7 mmol of **24**). The resulting dihydropyran **27** was then hydrogenated to give pyran intermediate **28**. Acetylation of the second alcohol and concomitant inversion of the configuration was achieved via mesylation/S_N2 substitution in a two-step sequence.[8] Finally, oxidation of the acetal functionality of **29** to a lactone was effected by

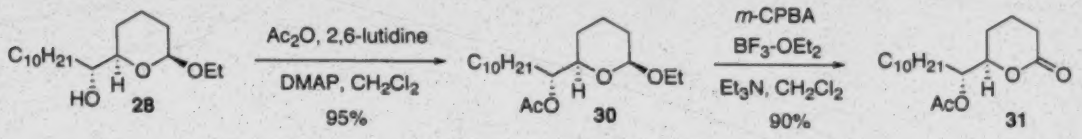
treatment with *m*-CPBA in the presence of BF_3-OEt_2[9] followed by Et_3N, giving **1**.[10] It was found that the addition of Et_3N is essential for the reaction. Otherwise, a mixture of starting material and a number of side products were obtained after reaction work-up. The NMR spectroscopic data and the absolute configuration of synthetic **1** are in full agreement with the reported data of natural **1**. Thus, the catalytic asymmetric synthesis of **1** was accomplished. Moreover, the absolute configuration of dihydropyran **27** was determined to be 1*S*, 5*R* and 6*R* based on the synthesis.



Scheme 4.6

The synthesis of (5*R*, 6*R*)-6-acetoxy-hexadecanolide, the C6 epimer of **1**, as illustrated in Scheme 4.7, is more straightforward compared to that of **1**. Reaction of

compound **28**, an intermediate in the synthesis of **1**, with Ac_2O in the presence of Et_3N and a catalytic amount of DMAP provided intermediate **30**. Oxidation of **30** under the same conditions as that of **29** afforded (5*R*,6*R*)-6-acetoxy-hexadecanolide **31**.



Scheme 4.7

4.4 Conclusion

In summary, the catalytic asymmetric syntheses of (5*R*,6*S*)-6-acetoxy-hexadecanolide (**1**) and (5*R*,6*R*)-6-acetoxy-hexadecanolide (**31**) were achieved by employing a three-component inverse electron demand hetero-Diels-Alder reaction as the key step. The synthesis of **1** was completed in seven steps from commercially available propionaldehyde diethyl acetal in 35% overall yield. The synthesis of **31**, which is more efficient, required six steps in 55% overall yield. Furthermore, the enantiomers of **1** and **31** can be synthesized in the same way by use the enantiomeric (1*R*,2*S*) Cr(III) catalyst. These concise routes clearly demonstrate the efficiency of our three-component methodology. Moreover, the absolute configuration of the α-hydroxyalkyl dihydropyrans, prepared by the three-component reaction using (1*S*,2*R*) Cr(III) catalyst, was determined to be 1*S*, 5*R* and 6*R* based on the synthesis of pheromone **1**.

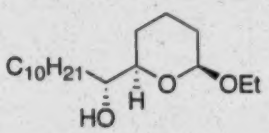
4.5 Experimental

4.5.1 General

The methods described in Section 3.6.1 also apply here.

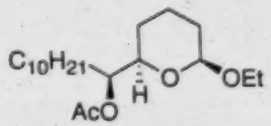
4.5.2 Experimental procedure

(1*R*)-((2*S*,6*R*)-6-Ethoxy-tetrahydro-pyran-2-yl)-undecan-1-ol (28)



Compound **27** (596 mg, 2.00 mmol) was dissolved in ether (10.0 mL) and Pd(C) (10% wt, 30.0 mg) was added. The reaction was stirred under an atmosphere of H_2 for 4 hours, then filtered through celite, and the celite washed with ether (20 mL). The ether was evaporated to give crude **28**. Purification by flash column chromatography (deactivated silica-gel, hexanes/ ether 9:1) led to the isolation of **28** (541 mg, 90%) as a clear oil. $[\alpha]^{23}_D$ +39.0 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) δ 3465, 2924, 1442, 1255; ^1H NMR (300 MHz, $CDCl_3$) 4.42 (dd, *J* = 2.1, 9.3 Hz, 1H), 3.86 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.42-3.60 (m, 2H), 3.25 (ddd, *J* = 2.1, 6.4, 11.1 Hz, 1H), 2.52 (d, *J* = 3.9 Hz, 1H), 1.76-1.96 (m, 2H), 1.22-1.58 (m, 25H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 102.2, 79.1, 73.8, 64.1, 32.7, 31.8, 31.2, 29.6, 29.5, 29.5, 29.3, 26.5, 25.3, 22.6, 21.9, 15.2, 14.0; HRMS (EI, *m/z*) calcd for $C_{18}H_{36}O_3$ 300.26645, found 300.26580.

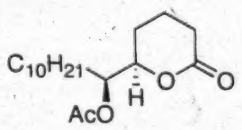
(1*S*)-Acetoxy-((2*S*,6*R*)-6-ethoxy-tetrahydro-pyran-2-yl)-undecan-methane (28)



To a stirred solution of **28** (284 mg, 0.950 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.270 mL, 1.50 mmol) and the solution was stirred at 0 °C for 30 minutes. Methanesulfonyl chloride (90.0 μL, 1.14 mmol) was added and the solution was stirred for additional 30 minutes. A saturated aqueous NH_4Cl solution (12 mL) was then added to the solution. The organic layer was separated and the aqueous layer extracted with ether (30 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude mesylate was used for the next reaction without further purification.

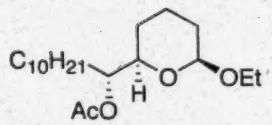
To the crude mesylate was added cesium acetate (640 mg, 3.30 mmol), 18-crown-6 (600 mg, 2.30 mmol) and toluene (10 mL). The reaction was allowed to stir at 100 °C for 24 hours. The solution was cooled to ambient temperature and concentrated. The residual oil was purified by flash column chromatography (deactivated silica-gel, hexanes/ether 19: 1) to give compound **29** (201 mg, 62%) as a clear oil. $[\alpha]^{23}_D$ +14.1 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 2926, 1743, 1441, 1201; ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (ddd, J = 3.6, 6.5, 8.4 Hz, 1H), 4.36 (dd, *J* = 9.2, 2.1 Hz, 1H), 3.82 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.50 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.36-3.42 (m, 1H), 2.02 (s, 3H), 1.22-1.96 (m, 27H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 102.2, 76.6, 75.5, 63.9, 31.8, 31.1, 30.4, 29.5, 29.5, 29.4, 29.2, 26.6, 25.0, 22.6, 21.8, 21.0, 15.1, 14.0; HRMS (ESI, *m/z*) calcd for $C_{20}H_{38}O_4Na$ 365.26623, found 365.26664.

(5*R*, 6*S*)-6-Acetoxy-5-hexadecanolide (1)



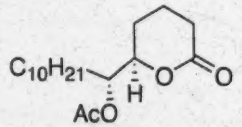
To a stirred solution of **29** (126 mg, 0.370 mmol) and *m*-chloroperoxybenzoic acid (pure, 182 mg, 0.480 mmol) in CH_2Cl_2 (2 mL) at 0 °C, was added dropwise BF_3-OEt_2 (50.0 μL, 0.400 mmol). The mixture was stirred for 10 minutes, followed by 1.5 hours at ambient temperature. The mixture was then cooled to 0 °C and Et_3N (0.260 mL, 1.85 mmol) was added slowly. The solution was allowed to stir at 0 °C for 2 hours, then poured into a mixture of saturated aqueous solutions of $NaHCO_3$ and NaS_2O_3. The mixture was extracted with ether (3 × 15 mL), the organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated. The residual oil was purified by flash chromatography (hexanes/ether 4:1) to give **1** (102 mg, 88%) as a clear oil. The spectral data are in full accord with the literature data. $[\alpha]^{23}_D$ –35.1 (c = 1.1, $CHCl_3$), Lit.[3c] $[\alpha]_D$ -37.4° (c = 2.2, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 2924, 1744, 1466, 1229; ^1H NMR (300 MHz, $CDCl_3$) δ 4.96-5.02 (m, 1H), 4.34 (ddd, *J* = 3.8, 4.9, 10.3 Hz, 1H), 2.56-2.62 (m, 1H), 2.39-2.51 (m, 1H), 2.06 (s, 3H), 1.20-1.95 (m, 22H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.3, 80.4, 74.2, 31.8, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 25.2, 23.4, 22.6, 20.9, 18.2, 14.0; HRMS (ESI, *m/z*) calcd for $C_{18}H_{33}O_4$ 313.23734, found: 313.23744.

(1*R*)-Acetoxy-((2*S*,6*R*)-6-Ethoxy-tetrahydro-pyran-2-yl)-undecan-methane (28)



To a 25 mL rbf was added **29** (194 mg, 0.650 mmol), 2,6-lutidine (0.100 mL, 0.980 mmol) and DMAP (7.90 mg, 0.065 mmol) in dry CH_2Cl_2 (2 mL). The mixture was cooled to 0 °C and acetic anhydride was added via a syringe (0.060 mL, 0.650 mmol). The reaction mixture was stirred at 0 °C for 1 hour and further stirred at ambient temperature overnight. Water (10 mL) and ether (10 mL) were added to the solution. The phases were separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with a saturated solution of NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash column chromatography (deactivated silica-gel, hexanes/EtOAc 9:1) to provide **30** (225 mg, 95%) as a clear oil. $[\alpha]^{23}_D$ +48.8 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2, cast, cm^{-1}) 2925, 1739, 1457, 1201; ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 (ddd, J = 4.4, 5.4, 8.0 Hz, 1H), 4.36 (dd, *J* = 9.3, 2.1 Hz, 1H), 3.82 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.42-3.56 (m, 2H), 2.06 (s, 3H), 1.22-1.96 (m, 27H), 0.88 (t, *J* = 6.8Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 102.5, 76.1, 74.9, 64.0, 31.8, 31.2, 29.9, 29.5, 29.5, 29.4, 29.4, 29.3, 26.0, 25.3, 22.6, 22.0, 21.0, 15.2, 14.0; HRMS (EI, *m/z*) calcd for $C_{20}H_{38}O_4Na$ 365.26623, found 365.26634.

(5*R*, 6*R*)-6-Acetoxy-5-hexadecanolide (31)



To a stirred solution of **30** (126 mg, 0.370 mmol) and *m*-chloroperoxybenzoic acid (182 mg, 0.480 mmol) in CH_2Cl_2 (2 mL) at 0 °C, was added dropwise BF_3-OEt_2

(50.0 μL, 0.400 mmol). The mixture was stirred for 10 minutes, followed by 1.5 hours at ambient temperature. The mixture was then cooled to 0 °C and Et_3N (0.260 mL, 1.85 mmol) was added slowly. The solution was allowed to stir at 0 °C for 2 hours, then poured into a mixture of saturated aqueous solutions of $NaHCO_3$ and $Na_2S_2O_3$ (10 mL). The mixture was extracted with ether (3 × 15 mL), the organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated. The residual oil was purified by flash chromatography (hexanes/EtOAc 5:1) to give **32** (105 mg, 90%) as a clear oil. The spectral data are in full accord with the literature data. $[\alpha]^{23}_D$ +14.2 (c = 2.0, $CHCl_3$), Lit.[3c] $[\alpha]_D$ 14.6° (c = 2.2, $CHCl_3$) IR (CH_2Cl_2, cast, cm^{-1}), 2925, 1739, 1457, 1201; ^1H NMR (300 MHz, $CDCl_3$) δ 4.96-5.02 (m, 1H), 4.35 (ddd, *J* = 3.4, 3.4, 11.3 Hz, 1H), 2.39-2.68 (m, 2H), 2.06 (s, 3H), 1.56-1.98 (m, 6H), 1.18-1.28 (m, 17H), 0.82 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.6, 79.7, 73.8, 31.8, 29.9, 29.6, 29.5, 29.5, 29.4, 29.3, 29.3, 25.3, 24.1, 22.6, 20.9, 18.4, 14.1; HRMS (EI, *m/z*) calcd for $C_{18}H_{33}O_4$: 313.23788, found: 313.23673.

4.6 References

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Chapter 5

Catalytic enantioselective synthesis and evaluation of one member of the thiomarinol family of potent antibiotics and simplified analogues.

5.1 Introduction

Antibiotics are a class of drugs that fight infections caused by bacteria. Since their discovery in the 1930s,[1] antibiotics have dramatically reduced illness and saved the lives of millions of people around the world from infectious diseases. However, mankind's war with bacteria is far from over. In fact, its ending may never be reached due to the evolution of bacteria that leads to antimicrobial resistance.[2] Given the huge number of bacteria types, along with their rapid growth cycles and high gene mutation frequencies, antibiotic resistance is developing very fast. In addition, the worldwide overuse and misuse of antibiotics further promotes resistance among bacteria, again aggravating serious disease. As a result, superbugs, bacteria that resist the most powerful antibiotics, are increasingly being reported and the rise in deaths is proportional to this increase. For this reason, there remains a significant need for new antibiotics that provides efficient therapy.

A strategy that has been used frequently in developing alternate antibiotics has been the refinement of existing antibiotic structures through chemical modifications. For example, the semisynthetic modification of cephalosporins has led from first generation (cephazolin) to second (cefoxatin) to third (ceftriaxone) and now fourth (cefipime)

generation (Figure 5-1) version where the bicyclic lactam core scaffold is maintained and the chemical modification on side chains lead to improved activity especially against resistant bacteria. Similarly, the natural macrolide antibiotic erythromycin was chemically modified to give the second generation semisynthetic azithromycin and clarithromycin and now the third generation of ketolides such as cethromycin and telithromycin.

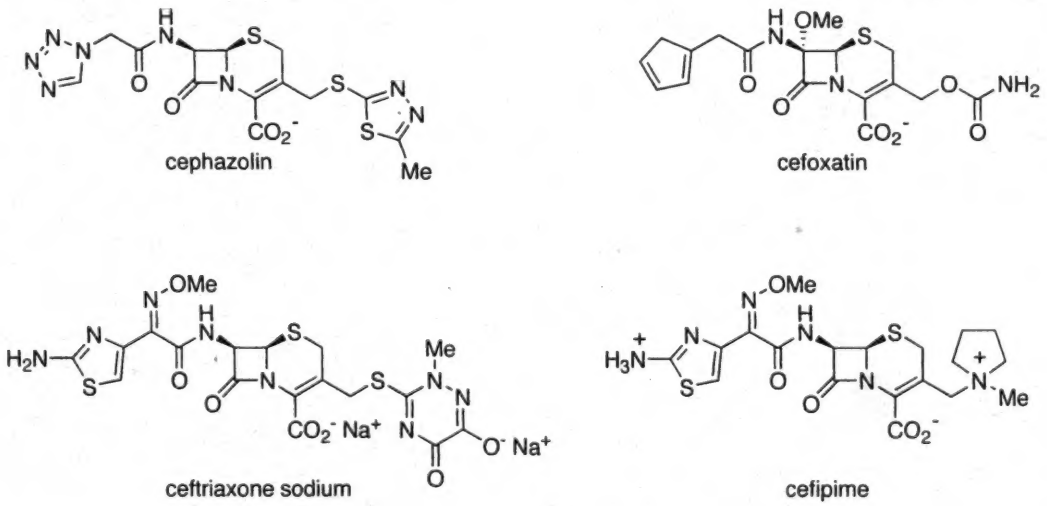
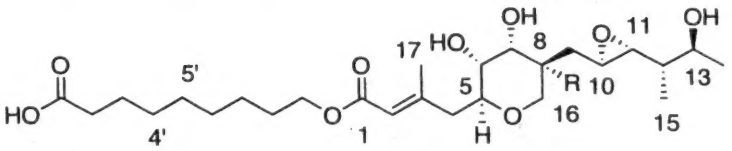


Figure 5-1. Derivatives of cephalosporin antibiotics

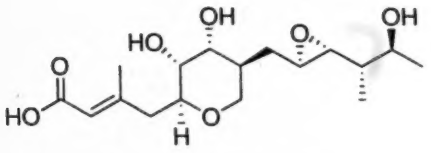
Pseudomonic acids, produced by *Pseudomonas fluorescens*, are a family of C-glycopyranoside antibiotics and potent inbibitors of Gram-positive0 aerobic bacteria. The antibiotic extract of *P. fluorescens* is a mixture of compounds comprised of 90% pseudomonic acid A, 8% pseudomonic acid B, and less than 2% of pseudomonic acid C an D.[3a, 3b, 3c] All four pseudomonic acids possess the same central pyran ring with the major structural difference of these compounds lying in the functionalities of the C5 and C8 side chains (Figure 5-2). Studies have shown that all four of the pseudomonic acids exhibit similar antimicrobial activity.



pseudomonic acid A: R=H (**1a**)
pseudomonic acid B: R=OH (**1b**)
pseudomonic acid C: R=H, C-10/C-11 *E*-alkene (**1c**)
pseudomonic acid D: R=H, C-4'/C-5' *E*-alkene (**1d**)

Figure 5-2. Structures of pseudomonic acids

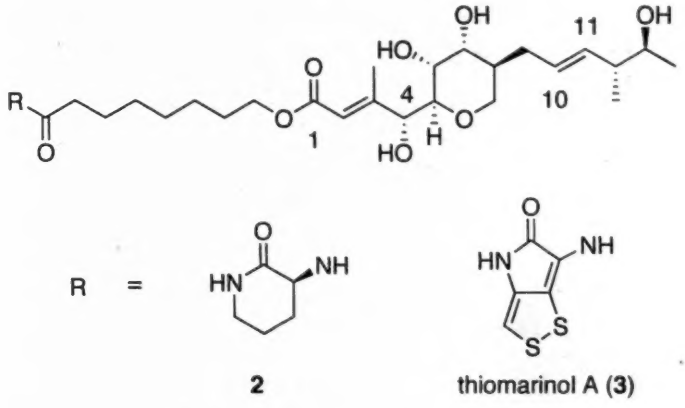
Since pseudomonic acid A (**1a**) is the major component of the antibiotic extracts, the main research effort of the drug industry has been focusing on developing this compound as a pharmaceutical agent. As a result, pseudomonic acid A (mupirocin) is clinically used as an antibiotic agent under the trade name of Bactroban®. Unfortunately, it displays poor bioavailbility due to the rapid hydrolysis of the C-1 ester upon entering the bloodstream, which produces the inactive monic acid A (Figure 5-3). As a consequence, the antibiotic has to be used topically and mainly for treatment of bacterial skin infections. Another main drawback of pseudomonic acid A is that it is highly bound to human serum protein to an extent of 95%. Since only the unbound portion of an antibiotic is free to exert any antibacterial action, this undesired property further reduces the antimicrobial efficacy of pseudomonic acid A. Consequently, there has been significant interest in the development of improved, less toxic analogues that could also be suitable as bloodstream antibiotics.[3d]



monic acid A (**1e**)

Figure 5-3. Structure of monic acid A

Thiomarinol A (**3**), and one of its derivatives, **2**, are rare marine natural products recently isolated from the bacterium *Alteromonas rava* sp. Nov. SANK 73390.[4a, 4b] Their structures were determined to be derivatives of pseudomonic acid C (**1c**), which displays similar antimicrobial activity to that of pseudomonic acid A (**1a**). The structures of **2** and thiomarinol A differ from pseudomonic acid C only by the presence of a C-4 hydroxyl and a shorter C-1 alkoxy chain. Compound **2** and **3** are distinguishable, respectively, by their holothin and anhydro-ornithine C-1 amide end group (Figure 5-4).



2 thiomarinol A (**3**)

Figure 5-4. Structures of thiomarinols

These natural substances were also found to be excellent antimicrobial agents. In one example, the activity of **2** against *S. aureus* was shown to be comparable to that of tetracycline and streptomycin.[4a] Thiomarinol A was found to be much more potent than

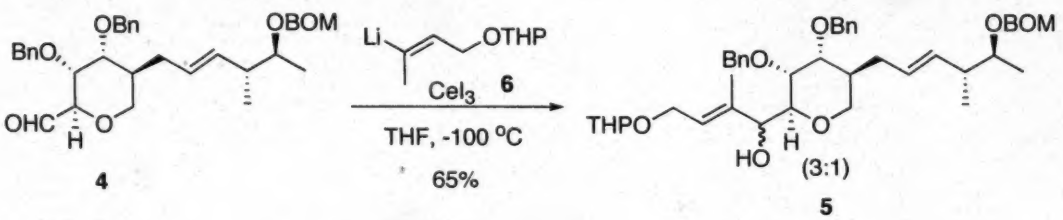
pseudomonic acid A and possesses a wider spectrum of activity (Gram-positive and Gram-negative bacteria).[4c] Thus, thiomarinaols are very attractive leads for antibacterial drug discovery.

One of the most important goals of modern natural product synthesis is that the researchers can employ their route not only to the desired bioactive natural product, but also to structural analogues, in an attempt to discover compounds with improved biological properties. For example, there are 15 syntheses (total and formal) of the pseudomonic acids reported in the literature along with hundreds of derivatives that were synthesized based on the chemistry developed during these synthetic studies.[3d, 5] However, at the outset of this project no total syntheses of any member of the thiomarinol family of antibiotics were reported in the literature. The impressive antimicrobial activity of these natural products stimulated us to develop an efficient synthetic route to the thiomarinols. In addition, we were also interested in producing analogues, based on the chosen synthetic route, which may display higher antimicrobial potency and oral bioavailability.

5.2 Reported synthetic studies toward the thiomarinols

Since the syntheses of anhydroornithine and holotin are known in the literature,[6] the major challenge in the synthesis of thiomarinols is the construction of the right hand central pyran structure containing the C5 and C8 side chains. This part of the molecule possesses seven stereocentres including five contiguous ones around the pyran ring (C4-

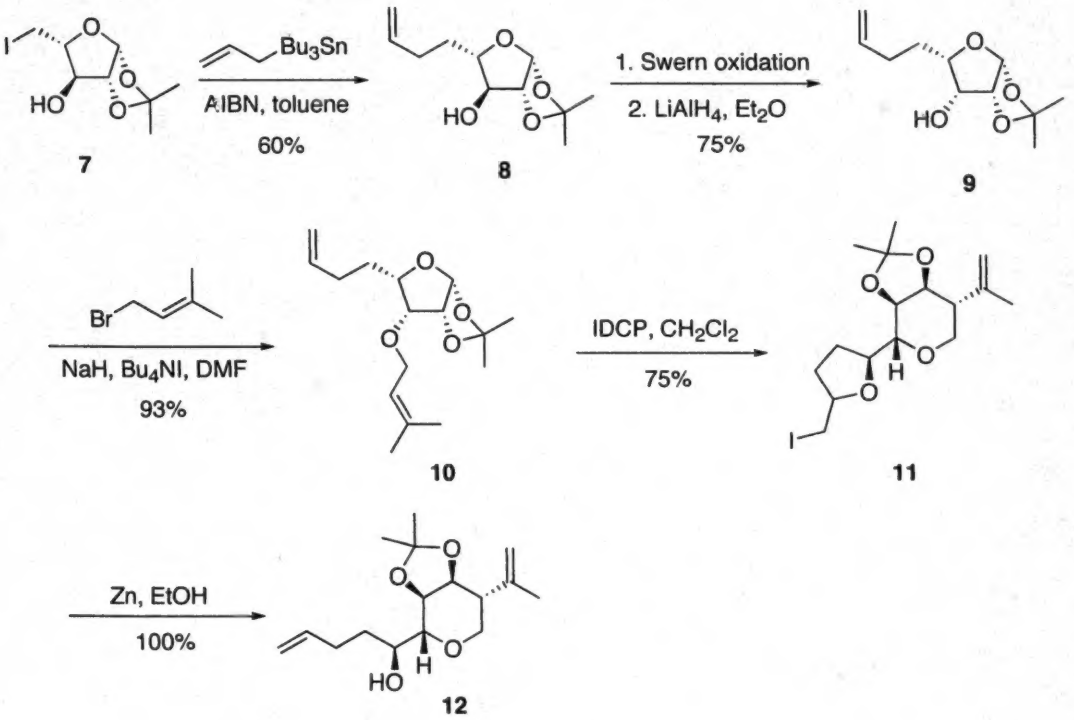
C8). In particular, stereocontrol at C4 represents a significant synthetic challenge. In their synthesis of pseudomonic acid C, Williams and co-workers used a nucleophilic addition reaction to construct the C4 and C5 carbon-carbon bond.[7] In this reaction, the organic cerium species **6** added to the aldehyde **4** to provide the alcohol **5** in 65% yield as a 3:1 mixture of C4 epimers (Equation 5-1). In their route, both of the epimers could be transformed to pseudomonic acid C *via* a deoxygenation sequence, however, the result from this study highlighted the difficult stereocontrol at C4 of the thiomarinols by utilizing a nucleophilic addition approach.



Equation 5-1

At the beginning of our synthetic studies, a single paper reported by Mootoo and co-workers was the only known attempt toward the thiomarinols.[8] The key reaction in their study is an oxocarbenium ion cyclization reaction. Specifically, 5-deoxy-5-iodo-1,2-*O*-isopropylidene-β-L-*arabino*-furanose **7** was converted to **8** via a Keck allylation. Oxidation of the hydroxyl group at C3 followed by reduction of the resulted ketone inverted the stereocenter, providing **9**. This was then alkylated under phase transfer conditions giving **10** in 93% yield. Treatment of **10** with iodo(bis)collidine perchlorate (IDCP) provided the oxocarbenium ion cyclization product **11** as a single isomer. The tetrahydrofuran ring in **11** was subsequently opened *via* a zinc mediated reductive elimination to afford **12**. The configurations of the five stereocentres around the pyran

unit of **12** are the same as those of the five contiguous stereocentres in the enantiomers of thiomarinols (Scheme 5.1). The enantiomer of **12** that possesses the same stereochemistry as that of the thiomarinols could be prepared from D-arabinose following identical procedures.



Scheme 5.1

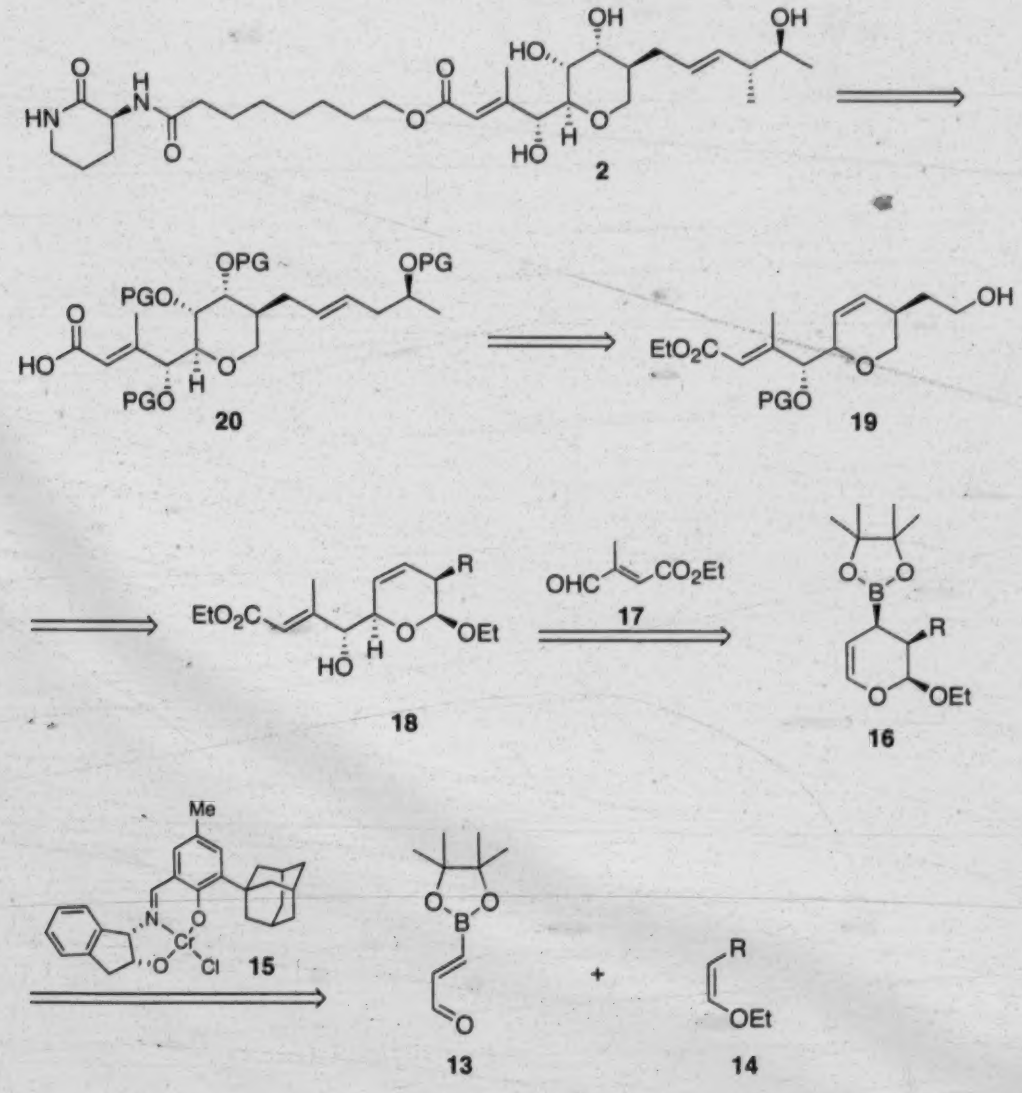
5.3 Our synthetic plan to the thiomarinols.

Over many years, our group has developed a longstanding interest in the development and application of multicomponent reactions in organic synthesis. As was discussed in Chapter 3, we developed the first catalytic enantioselective inverse electron demand [4+2] cycloaddition/allylboration reaction to construct α-hydroxyalkylpyrans.

We wished to test the suitability of 2-substituted enol ethers in the three-component reaction and apply it in the total synthesis of **2**.

We envisioned that the pyran core and the C-4 hydroxyl group of compound **2** could be constructed stereoselectively with an *endo*-selective hetero [4+2] cycloaddition/allylboration approach from 3-boronoacrolein pinacolate **13**, a suitably functionalized (*Z*)-2-substituted enol ether of type **14** and the commercially available aldehyde **17**. It is known, however, that 2-substituted enol ethers are difficult substrates in inverse electron demand Diels-Alder cycloadditions because of the added steric hindrance at the 2-position.[9] Our work with **13** previously highlighted its exceptional reactivity as a heterodiene,[10] which we hoped could overcome the low reactivity of the 2-substituted enol ether as a dienophilic partner. Since 2,3-dihydrofuran, one of the dienophile candidates, proved to be a poor reaction partner in the cycloaddition reaction (c.f. Chapter 3), our choice of dienophile was limited to acyclic 2-substituted enol ethers. From intermediate **19**, functional group manipulation of the R group and acetal reduction would provide compound **20**.[11] It was anticipated that the chemo- and stereoselective dihydroxylation would occur from the opposite face of the C5 and C8 side chains to provide the correct functionalization of the pyran ring. The C10-C11 trans double bond in the C8 side chain was planned to be constructed using a Julia-Kocienski olefination,[12] and the requisite C12-C13 propionate fragment could be accessed via either a Brown crotylboration[13] or the catalytic allylboration system developed in our group.[14] In the final step, hydrolysis of the ester, re-esterification with the side chain alcohol and final deprotection steps would afford the natural product **2** (Scheme 5.2). In a similar way,

thiomarinol A could also be synthesized by simply changing the alcohol side chain in the re-esterification step.

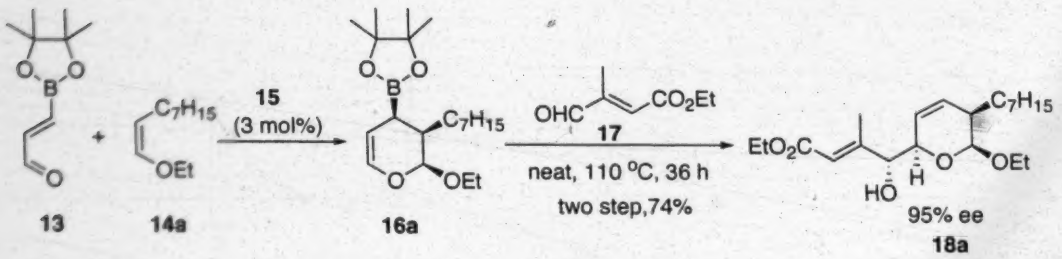


Scheme 5.2

5.4 Results and discussion

5.4.1 Model study

As discussed above, central to our synthetic strategy was the hetero [4+2] cycloaddition/allylboration reaction involving an acyclic 2-substituted enol ether to construct the pyran core structure. However, to the best of our knowledge, there are no reported examples of acyclic 2-substituted enol ethers being used in catalytic enantioselective inverse electron demand Diels-Alder reactions. As a preliminary study, we synthesized the simple enol ether **14a** using a literature procedure[15] and examined its behavior in the hetero-Diels-Alder cycloaddition/allylboration reaction as a model. To our delight, the final product was obtained in 74% yield with >98% de and 95% ee. The cycloaddition reaction was indeed more difficult with **14a** than with ethyl vinyl ether. Whereas the cycloaddition between ethyl vinyl ether and **13** is complete in 1.5 hours using 1 mol% of catalyst **15** at 20 °C, the cycloaddition between **14a** and **13** required five hours with 3 mol% of catalyst at the same temperature. Nonetheless, the all-*cis endo* adduct **16a** was cleanly formed as a single stereoisomer. To our surprise, it was the allylboration step that proved problematic. An astonishing temperature of 110 °C was needed to produce **18a** from **16a** and **17** in neat conditions. As a result, the tandem process could not be performed in "one-pot", and we found it necessary to remove catalyst **15** with a quick silica filtration in order to afford a clean allylboration product (Scheme 5.3).



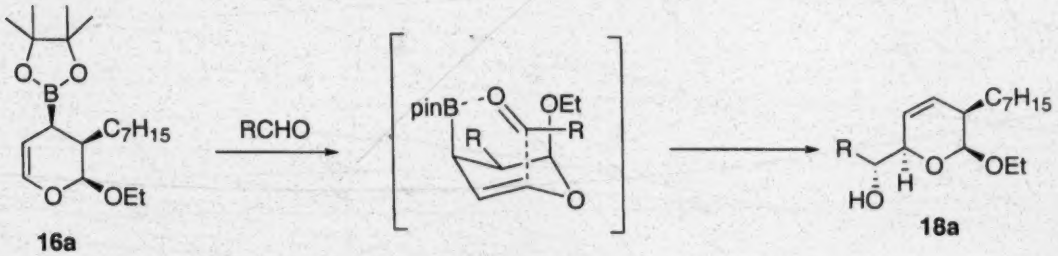
Scheme 5.3

To elucidate the stereochemistry of the final product, a great deal of effort was made to derivatize **18a** in order to obtain a single crystal for X-ray crystallographic analysis. Unfortunately, this proved not to be possible. In the end, we conducted an NMR study on compound **21a**, which was prepared by treating **18a** with TIPSOTf (Scheme 5-5).[16] The nOe result indicates the all-*cis* relationship of the three side chains on the pyran ring (Figure 5-5). At that time, we had no further evidence on the stereochemistry of C4 and as such, the stereochemistry of C4 was tentatively assigned as that of **18a** based on the precedent examples of products of allylboration reaction of cyclic allylboronates (c.f. Chapters 1, 2, 3).

Figure 5-5. nOe result of compound **21a**

In the putative allylboration transition state leading to **18a**, the ring assumes an unfavorable chairlike conformation with both boronate and ethoxy substituents in *pseudo* diaxial positions. It is possible that gauche interactions from the C8 chain (C_7H_{15}) further

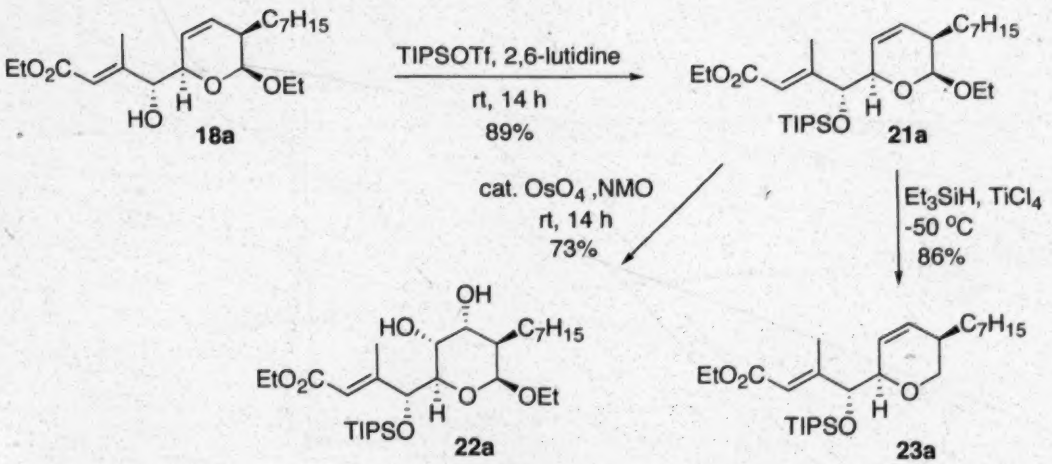
increase the barrier for conformational change, which could explain the high temperature needed for the allylboration step (Scheme 5.4). The C4-C5 stereochemistry can be explained by a chairlike transition state as shown previously.



16a **18a**

Scheme 5.4

Using compound **21a**, we further tested two important transformations, namely reduction of the acetal and the dihydroxylation of the cyclic double bond, which were planned in the synthesis of the targeted natural product. We were pleased to find that the acetal in **21a** could be reduced in high yield using Et_3SiH as reducing reagent and $TiCl_4$ as a Lewis acid promoter at a low temperature to provide **23a**.[11] Furthermore, ring dihydroxylation occurred chemo- and stereoselectively to afford the expected compound **22a** as a single isomer (Scheme 5.5).



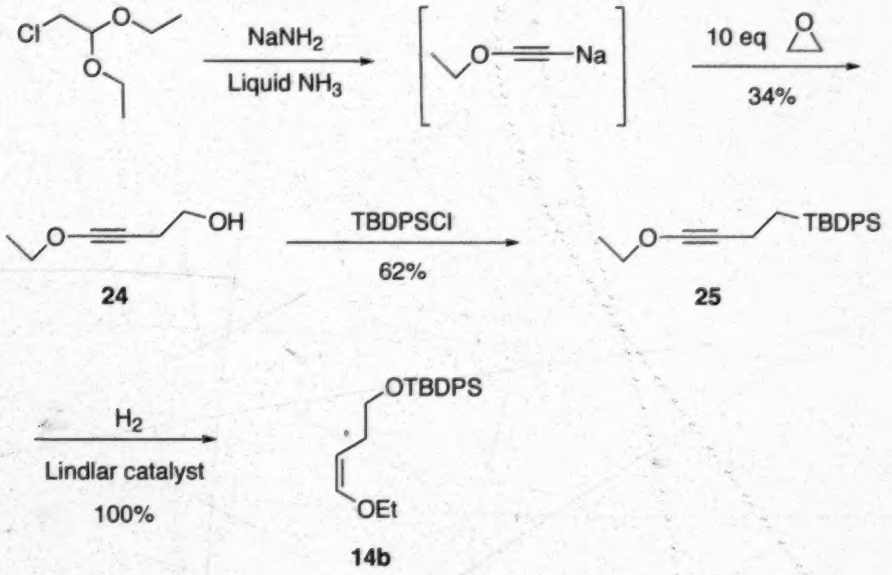
Scheme 5.5

5.4.2 Design and synthesis of the dienophile used in the synthesis of 2

To introduce the C8 side chain, we chose a 2-substituted ethyl enol ether in which the 2-substituent could be transformed into the Julia-Kocienski coupling precursor. To this end, we designed two kinds of enol ethers (Figure 5-6). The Type I enol ethers possess a protected alcohol at the 2-position of the side chain, which could be transformed to the sulfone precursor for the Julia-Kocienski coupling. The Type II enol ethers embody another type of functional group at the 2-position of the side chain, which could then be selectively transformed to a hydroxyl group.

Figure 5-6. Desired dienophiles for the synthesis of thiomarinols

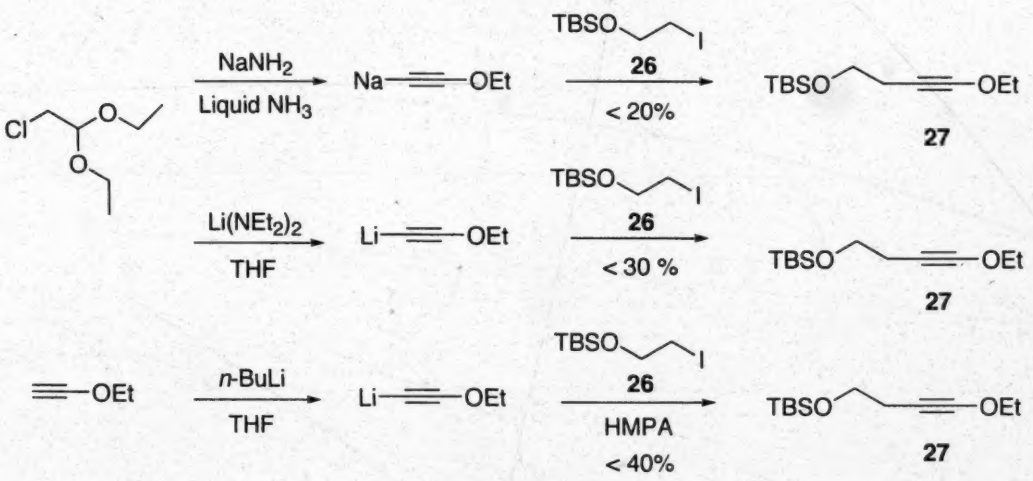
At the outset, we decided to synthesize enol ethers of Type I as the synthesis would be a few steps shorter than that using Type II enol ether, While there is one approach to this type of enol ether reported by Overman and co-workers in 1989 (Scheme 5.6),[17] the sequence requires nine equivalents of ethylene oxide and the overall yield is only 21%. Thus, it was considered not to be efficient enough to be applied to our synthesis.



Scheme 5.6

A great deal of effort was spent trying to develop an efficient route to Type I enol ethers. At the outset, we planned to make **27**, which could be transformed to **14c** via hydrogenation under Lindlar's conditions, by alkylation of the ethyl ethynyl anion with electrophile **26**. In an approach similar to Overman's, we first tried generating the ethyl ethynyl ether anion *in situ*, through treatment of chloroacetaldehyde diethyl acetal with $NaNH_2$ in liquid ammonia, then trapping the formed anion with a suitable electrophile

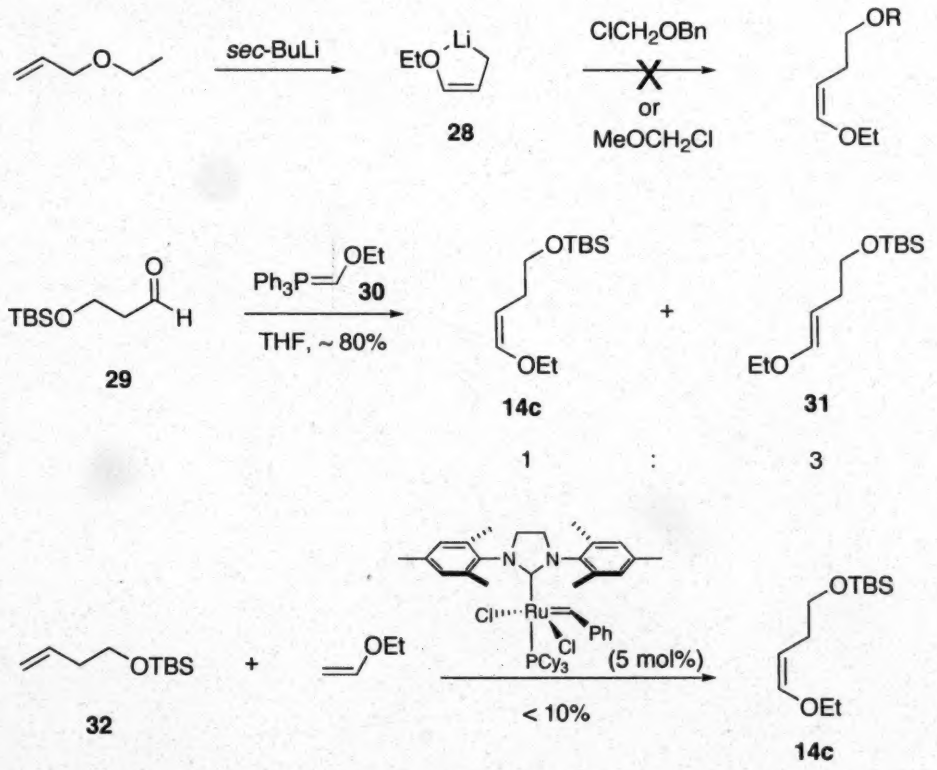
(Scheme 5.7). However, the yield of this sequence is extremely low (< 20% by crude ^{1}H-NMR).[18] Similarly, using $LiEt_2N$ to generate the ethyl ethynyl ether anion, and then trapping with electrophile **26**,[19] it was found that a significant amount of chloroacetaldehyde diethyl acetal was unreacted and the alkylation reaction proceeded in low yield. It was thought that the inefficiency in the generation of the ethyl ethynyl anion from chloroacetaldehyde diethyl acetal might be responsible for the low yield of the sequence. Thus, the anion was prepared by deprotonation of ethyl ethynyl ether with BuLi,[20] which is known to generate the corresponding acetylide anion quantitatively. Disappointingly, the alkylation reaction proved to be low yielding again.



Scheme 5.7

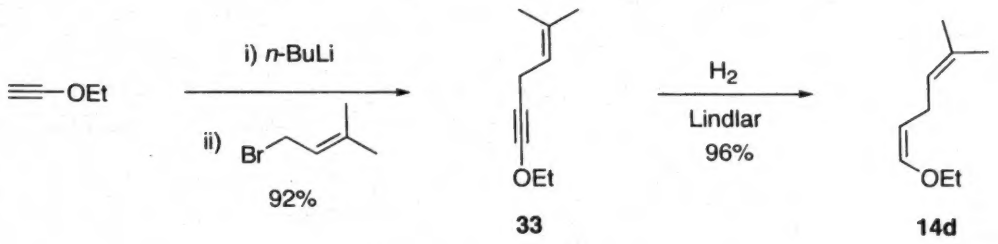
In addition to the alkylation reactions with the ethyl ethynyl anion, the alkylation of anion **28** with MOMCl and BOMCl, analogs to the synthesis of enol ether **14a**, did not provide any desired product (Scheme 5.8). Moreover, Wittig reaction[21] of aldehyde **29** with phosphorane **30** gave the undesired *E*-enol ether **31** as the major product and cross

olefin metathesis[22] of **32** with ethyl vinyl ether also proved to be an inefficient method to make desired enol ether **14c**.



Scheme 5.8

At this stage, we decided to synthesize the masked enol ether **14d**, a Type II enol ether. The functionality in **14d** was chosen to be a trisubstituted double bond, which is known to be selectively transformed into an alcohol group in the presence of a *cis*-double bond *via* a Sharpless AD[23]/oxidative cleavage/reduction procedure. Gratifyingly, it was found that **14d** could be made in only two steps in 92% overall yield *via* an alkylation[20]/Lindlar hydrogenation[17] procedure from ethyl ethynyl ether (Scheme 5.9). Impressively, no column chromatography separation was required in this synthesis of **14d**.

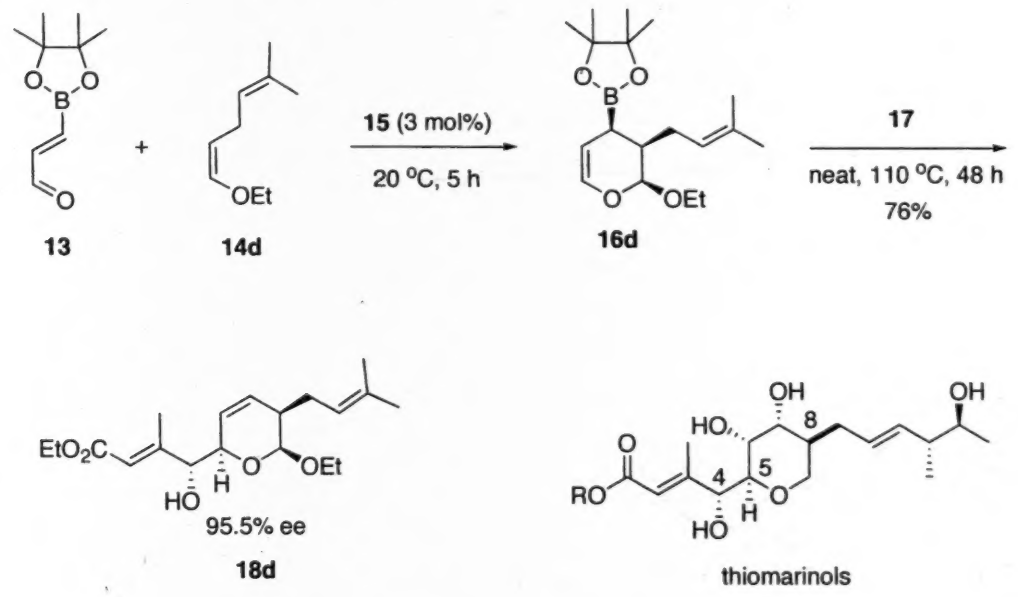


Scheme 5.9

5.4.3. Optimization of the key Diels-Alder cycloaddition/allylboration sequence

In the HDA reaction between 1-boronoacrolein pinacolate (**13**) with ethyl vinyl ether, nine equivalents of a commercially available, non-expensive ethyl vinyl ether was used.[10] However, when using enol ether **14d** as the dienophile, which was prepared in two steps from expensive starting material, the use of a large excess of dienophile needed to be avoided from an economic point of view. We were pleased to discover that the amount of **14d** could be reduced to 1.5 equivalents without affecting the yield and enantioselectivity of the reaction (Scheme 5.10). Moreover, most of the excess **14d** could be recovered by a simple bulb-to-bulb distillation through which the low boiling point **14d** was separated from the HDA product **16d** and the catalyst **15**. In a similar fashion to the model study, the allylboration step was carried out using two equivalents of aldehyde **17** at 110 °C for 48 hours. Likewise, the [4+2] cycloaddition/allylboration procedure could not be performed in "one-pot" and it was necessary to remove the catalyst with a short column. Once again, most of the excess of low boiling point aldehyde **17** could be recovered via a bulb-to-bulb distillation. Overall, the highly functionalized pyran **18d**, containing four stereocentres, was synthesized in 76% yield with >98% de and 95% ee

using almost equimolar amounts of **13**, **14d** and **17** in two separate but consecutive operations. Moreover, the sequence could be easily carried out on a multi-gram scale (3.2 g of **18d**). Remarkably, all three key stereocenters in the thiomarinols, C4, C5, and C8 are set in this process.

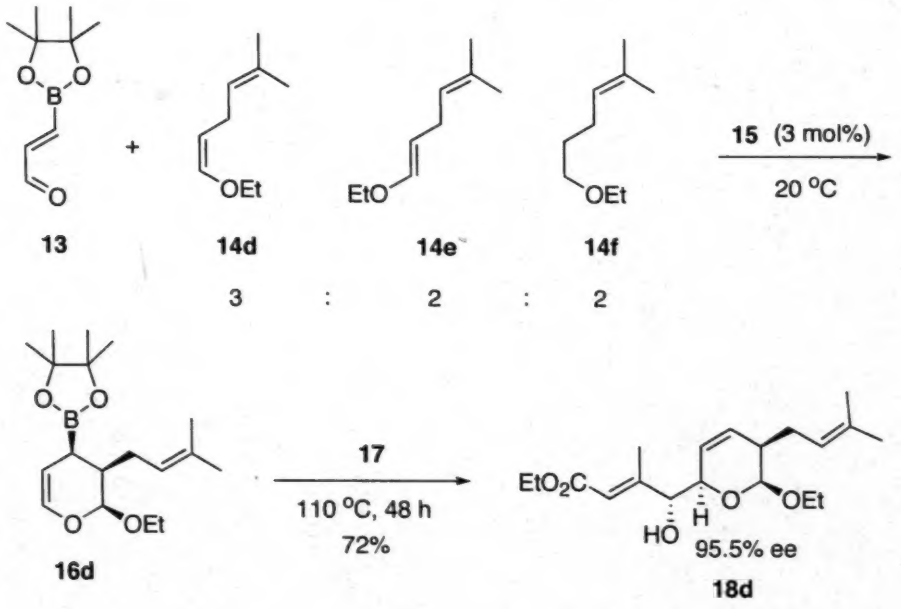


Scheme 5.10

5.4.4. Catalyst-controlled Z-enol ether selectivity in the cycloaddition reaction catalyzed by Jacobsen's chiral Cr(III) complex

Obtaining isomerically pure *Z*-enol ether **14d**, especially on large scale, proved to be problematic. The hydrogenation of **33** often provided a mixture of the *Z*-enol ether **14d**, *E*-enol ether **14e** and also the over-reduced ether **14f**. Fortunately, the *Z*-isomer **14d** was found to be more reactive than the *E*-isomer **14e** in the HDA reaction when using Jacobsen's Cr(III) catalyst (**15**). Reactions performed using a mixture of isomers mainly afforded the product consistent with a kinetically selective cycloaddition of the *Z*-isomer.

For instance, the cycloaddition reaction of **13** with a mixture of **14d**, **14e** and **14f** (3 : 2 : 2) in the presence of a catalytic amount of **15** almost exclusively gave the cycloadduct **16d** from the *Z*-enol ether **14d** (Scheme 5.11). Only a trace amount (< 3 mol%) of cycloadduct from the *E*-enol ether **14e** was observed. The cycloadduct **16d** underwent a further allylboration reaction with aldehyde **17** to afford **18d** without erosion of the enantioselectivity.



Scheme 5.11

To explore the origin of the *Z*/*E* enol ether selectivity in the HDA reaction, we compared the cycloaddition reaction of 1-boronoacrolein pinacolate (**13**) with a 3 : 1 mixture of *Z*-**34** and *E*-**34** using either catalyst **15** or a standard achiral catalyst, $Yb(fod)_3$[23] (Scheme 5.12). While the HDA cycloaddition catalyzed by **15** exhibited *Z*-enol ether preference, the cycloaddition catalyzed by $Yb(fod)_3$ did not show any selectivity between the *Z*- and *E*- isomers. Therefore, it appears that the huge catalyst **15**

provides steric control that leads to faster consumption of *Z*-2-substituted enol ethers.[24] Furthermore, this selectivity is particularly useful in view of the difficult preparation of isomerically pure *Z*-2-substituted enol ethers. In fact, all the commercially available 2-substituted enol ethers are composed of a mixture of *Z*-and *E*- isomers.

The *Z*-enol ether selectivity in the inverse electron demand cycloaddition catalyzed by **15** could be explained by the working model proposed by Jacobsen and co-workers (Figure 5-7).[25] In the transition state, the aldehydes bind to the catalyst such that the formyl proton point away from the large adamantyl group and towards the aminoindanol oxygen, causing the oxabutadiene to occupy the same plane as the tridentate ligand. The area above this plane would essentially open while the area below the plane would be partially obstructed by the other component of the dimeric complex. The approach of the dienophiles would thus occur preferentially from the open area above the plane of the aldehydes. When using *E*-enol ether as the dienophile, the large R substituent would clash with the large adamantyl group. In contrast, in the transition state with *Z*-enol ether, the steric repulsion of a proton with adamantly group would be much smaller.

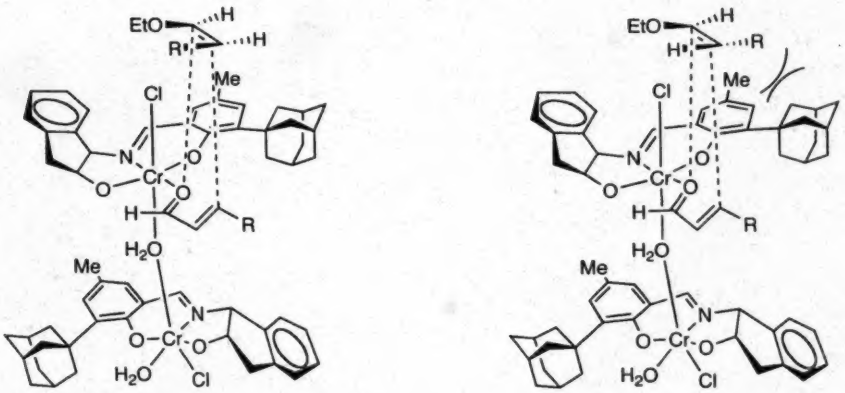
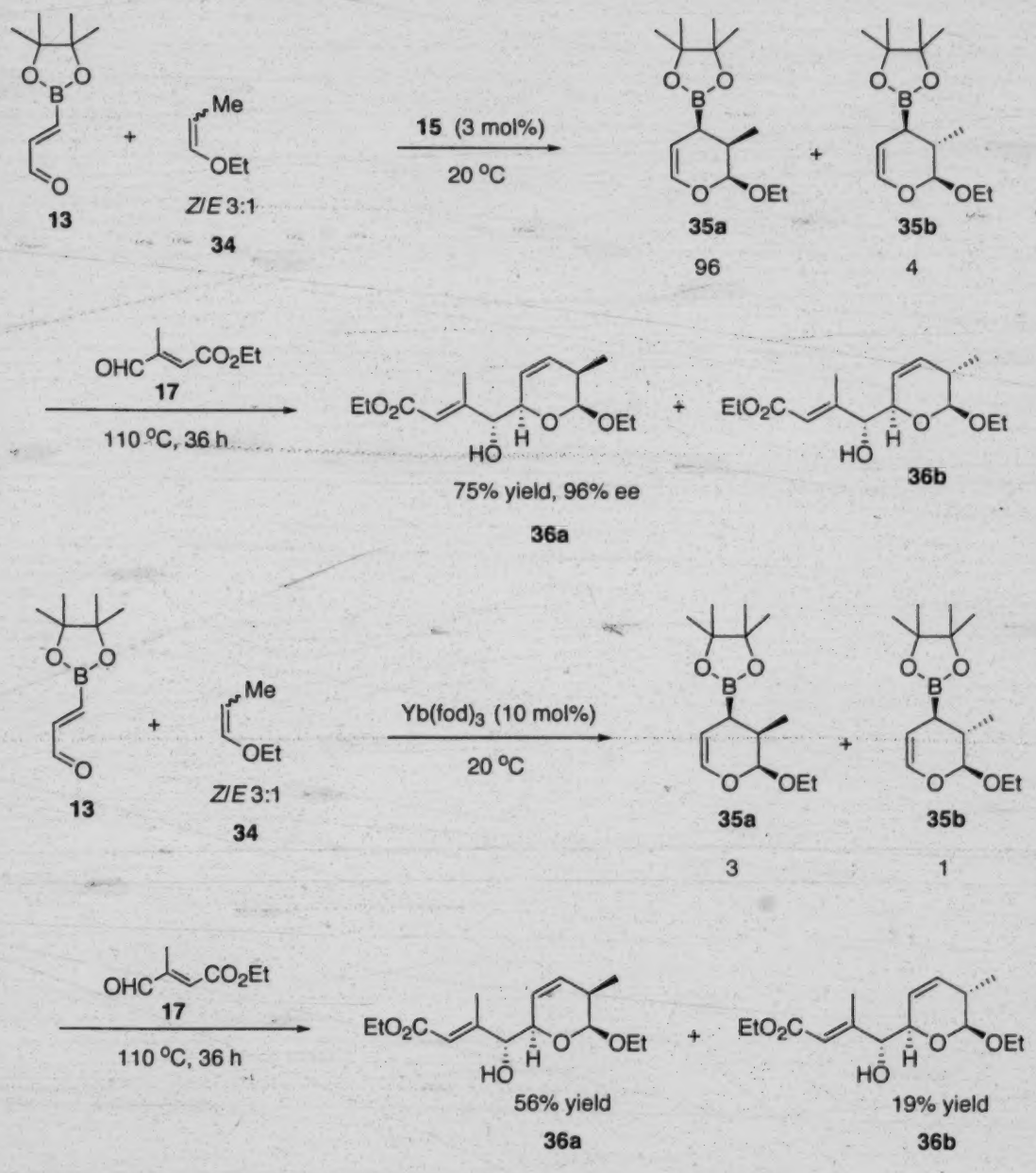


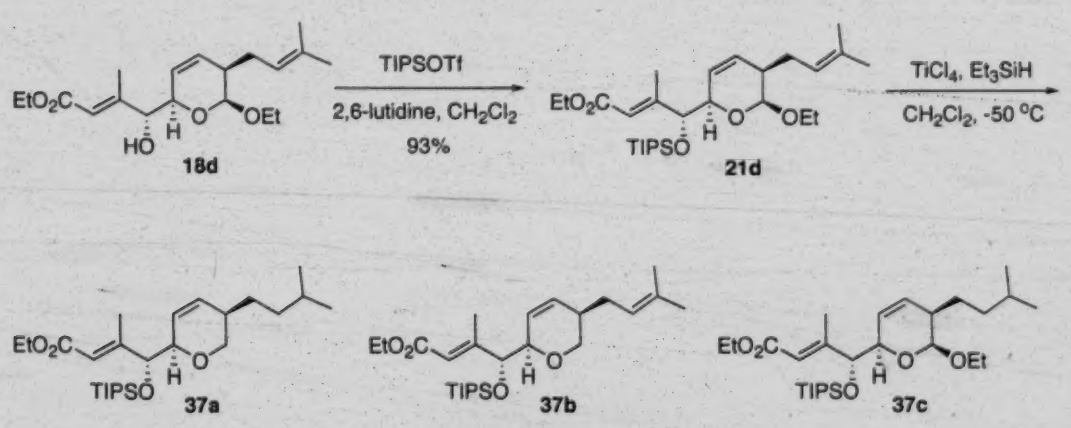
Figure 5-7. Transition states for the cycloaddition between α,β-unsaturated aldehydes and 2-substituted *Z*- and *E*-enol ethers catalyzed by **15**


13
Me
OEt
Z/E 3:1
34
15 (3 mol%)
20 °C
35a
96
35b
4
OHC
CO2Et
17
110 °C, 36 h
EtO2C
HO
H
O
OEt
75% yield, 96% ee
36a
36b
Yb(fod)3 (10 mol%)
3
1
56% yield
19% yield

Scheme 5.12

5.4.5 Total synthesis of 2

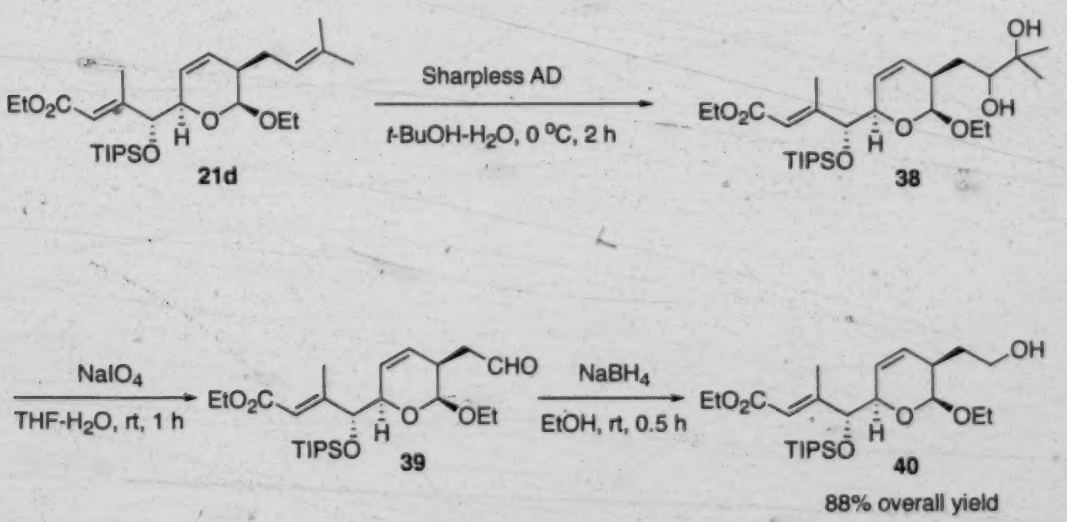
Having successfully developed an efficient sequence to key compound **18d**, the chemoselective reduction of the cyclic acetal in the presence of an electron-rich C10-C11 trisubstituted olefin, present in **18d**, was then explored. As such, following the protection of the secondary alcohol with a TIPS group, the resulting compound **21d** was treated with Et_3SiH and $TiCl_4$ at -50 °C, standard conditions for the reduction of an acetal.[11] Disappointingly, it was found that the trisubstituted olefin[26] was also reduced under these conditions, and a mixture of **37a**, **37b**, **37c** and other unidentified compounds were obtained as the products (Scheme 5.13). Variation of the Lewis acid and the reaction temperature did not improve the overall chemoselectivity.



Scheme 5.13

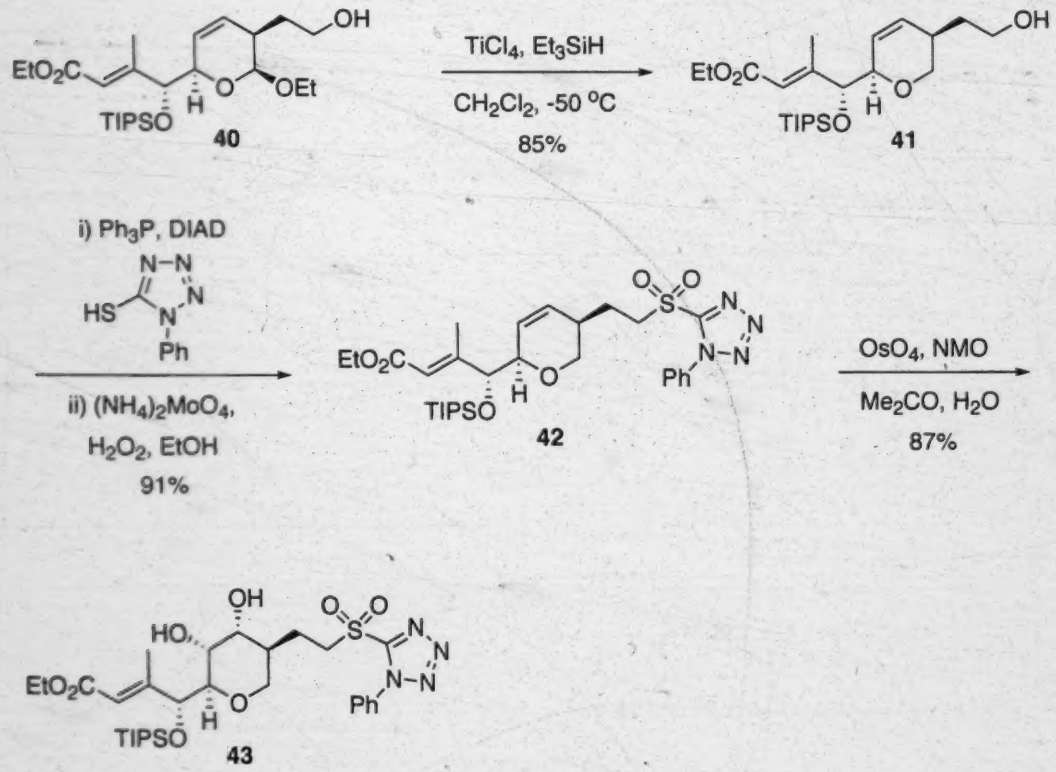
At this juncture, we decided to transform the C10-C11 trisubstituted olefin to an alcohol prior to the reduction. It has been shown that the rates for the Sharpless asymmetric dihydroxylation of isolated double bonds are much faster with trisubstituted olefins than with *cis*-1,2-disubstituted alkenes. Electronic factors also greatly influence

the rate of the Sharpless AD reaction and the rate with electron-rich olefins is much faster than with electron-poor olefins.[23] These properties of the Sharpless AD reaction are the basis for our selection of the C10-C11 trisubstituted olefin as a masked alcohol group in the presence of two other double bonds. As anticipated, the C10-C11 trisubstituted olefin was indeed selectively dihydroxylated under Sharpless AD conditions.[27] Next, the oxidative cleavage of the vicinal diol in **38** with $NaIO_4$[27] proceeded smoothly at ambient temperature, with subsequent reduction of the resulted aldehyde **39** with $NaBH_4$ in ethanol[28] to provide the desired alcohol **40** (Scheme 5.14). Although the overall sequence to transform the trisubstituted olefin to the alcohol group required a total of three linear steps, which might seem lengthy, it is important to note that the time-consuming chromatography purifications of intermediates **38** and **39** were avoided by using the crude compounds directly for the next transformations. As a result, the whole three-step sequence to compound **40** can be carried out within one day in an impressive overall yield of 88%.



Scheme 5.14

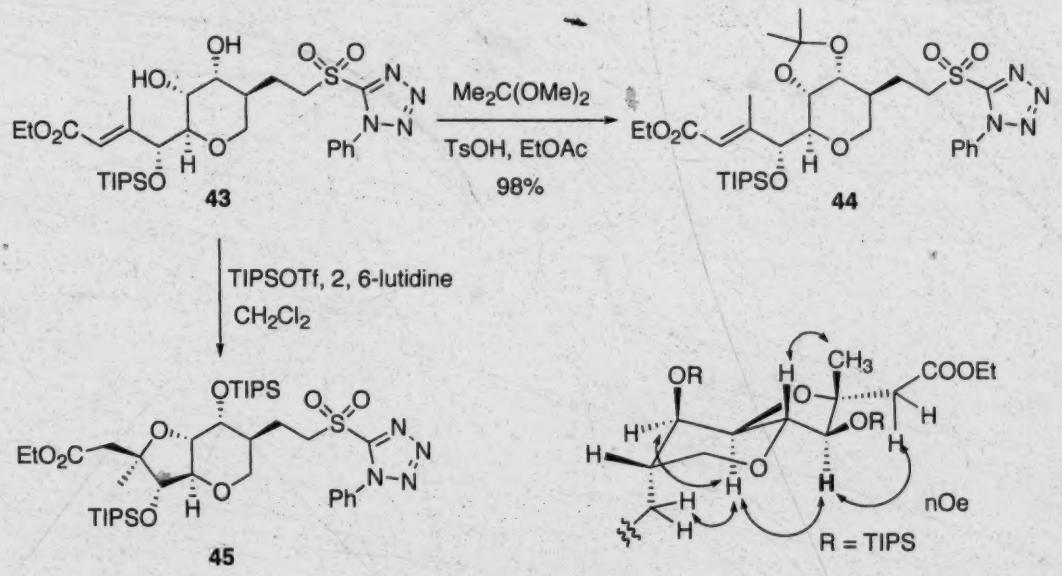
With alcohol **40** successfully synthesized, the stage was set to explore the reduction of the cyclic acetal group. Gratifyingly, the cyclic acetal was reduced using $TiCl_4$ and Et_3SiH[11] to provide compound **41** (Scheme 5.15). The hydroxyl group in **41** was then transformed into the tetrazolyl sulfone group required for a Julia-Kocienski coupling in "one-pot" *via* a Mitsunobu reaction followed by oxidation[29] to afford intermediate **42**. As originally envisaged, ring dihydroxylation[30] occurred selectively from the face opposite to the C5 and C8 substituents, providing **43**.



Scheme 5.15

As was discussed in the model study, the stereochemistry of C4 in the final product **18a** and **18d** from the [4+2] cycloaddition/allylboration sequence was not clear at that stage. It was tentatively assigned based on precedent examples of products of

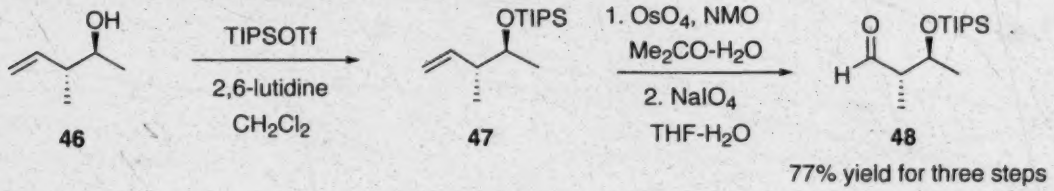
allylboration reaction of cyclic allylboronates. We planned to assign the configuration of C4 *via* the total synthesis of **2**. Fortuitously, when we attempted to protect the alcohol groups in intermediate **43** in their TIPS ether form, the bicyclic compound **45**, stemming from the intramolecular attack of the C6 hydroxyl group on the acrylate ester in **43**, was obtained as the major product in 88% yield (Scheme 5.16). The rigid nature of compound **45** allowed us to determine the configuration at C4 by a TROESY NMR experiment, and it was found to be the same as we anticipated.[4d] Having secured all the five stereocentres around the pyran core structure, protection of the vicinal alcohols as a cyclic ketal[31] afforded the sulfone precursor for the Julia-Kocienski coupling.



Scheme 5.16

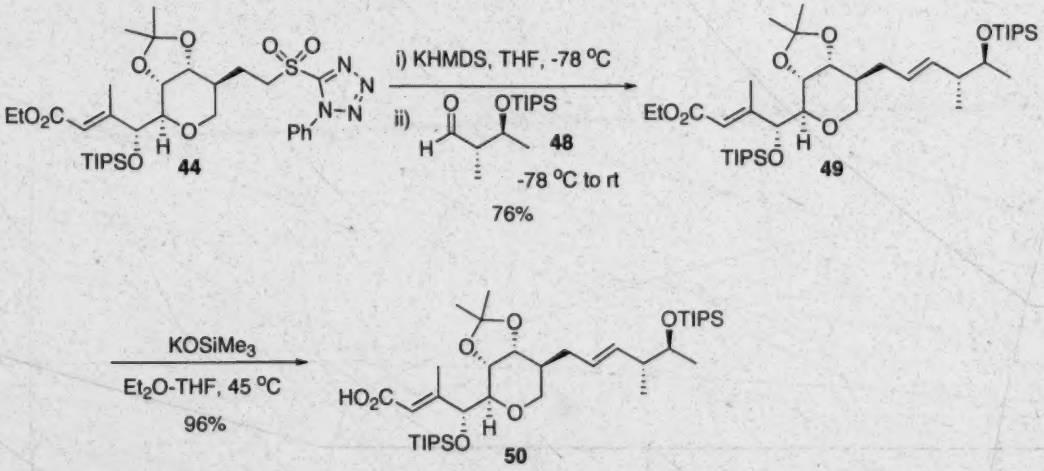
The synthesis of the aldehyde **48** required for the Julia-Kocienski coupling commenced with the protection of the known chiral homoallylic alcohol **46**, which was made *via* asymmetric Brown allylation.[13] Dihydroxylation of the terminal olefin with OsO_4/NMO, followed by cleavage of the newly installed diol with $NaIO_4$, gave the

desired aldehyde **48** in 77% overall yield starting from **46** (Scheme 5.17). Once again, tedious chromatography purifications of intermediates were avoided, with only one chromatography purification required for aldehyde **48** .



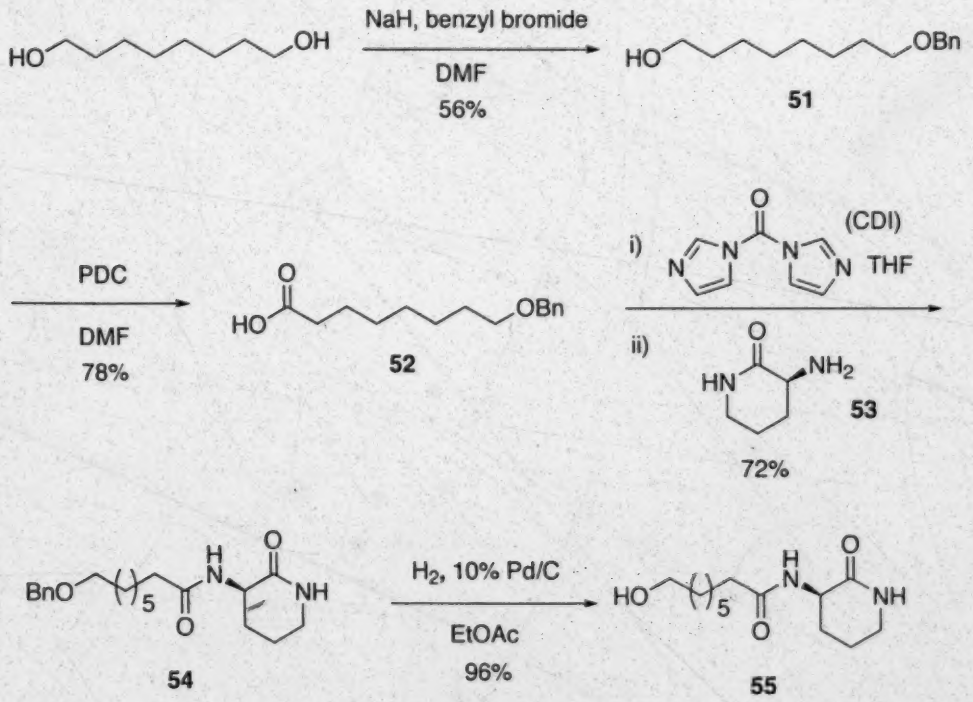
Scheme 5.17

With both **44** and **48** in hand, these fragments were smoothly joined under Julia-Kocienski coupling conditions to provide **49** in good yield with excellent *trans* selectivity.[32] Subsequent hydrolysis of the conjugated ester with $KOSiMe_3$[33] provided the acid **50** in 96% yield (Scheme 5.18). Overall, 3.2 g of **50** were obtained with ease, which is a clear testimony to the efficiency of the chosen synthetic sequence.



Scheme 5.18

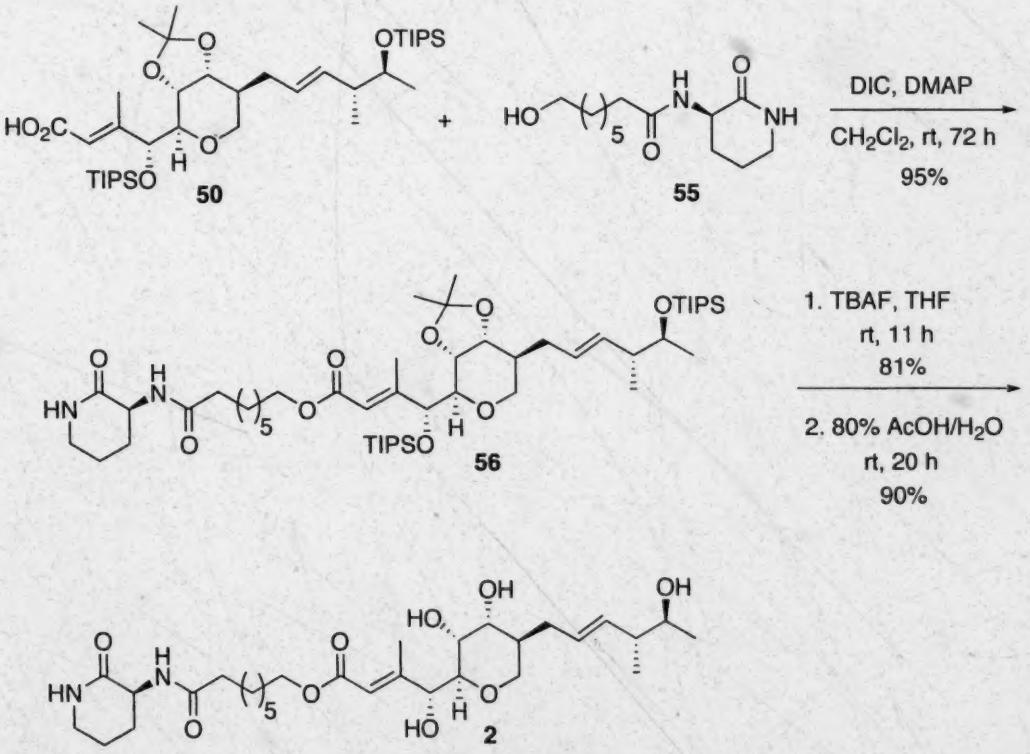
The synthesis of the alcohol building block **55** began from commercially available 1,8-octanol. Following monoprotection of the diol,[34] the unprotected hydroxyl group in **51** was oxidized to the carboxylic acid by PDC in DMF[35] to afford intermediate **52** in 72% yield. The subsequent coupling of **52** with known (*R*)-3-amino-2-piperidinone (**53**)[6d] employing CDI[36] in THF gave compound **53**. Finally, the benzyl protecting group in **50** was removed by hydrogenation to afford free alcohol **55** (Scheme 5.19).[37] Interestingly, **55** exhibits low solubility in EtOAc, and a significant amount of **55** remained on the surface of charcoal. As a result, washing the charcoal with a large amount of CH_2Cl_2 was essential to recover the product.



Scheme 5.19

With the two subunits **50** and **55** constructed, only a few operations remained before the total synthesis of **2** would finally be complete. As outlined in Scheme 5.20,

esterification of the acid **50** proceeded smoothly with alcohol **55** in the presence of DIC and DMAP[38] in CH_2Cl_2 to provide **56** in 95% yield. The two TIPS protecting groups were then removed with TBAF[38] in THF. Finally, deprotection of the ketal in $AcOH/H_2O$[31] completed the total synthesis of **2**.



Scheme 5.20

Since we could not obtain an authentic sample of natural **2**, the only way to determine if we actually had made the natural product is to compare the physical data of synthetic **2** with those of the natural one. It was found that the ^{1}H-NMR spectrum of our synthetic sample of **2** is identical to that of the natural **2**. Moreover, congruity was also seen in comparison of the mass spectra and optical rotation of the natural and synthetic **2**. However, the ^{13}C-NMR spectrum of the synthetic **2** in $CDCl_3$ first appeared to be

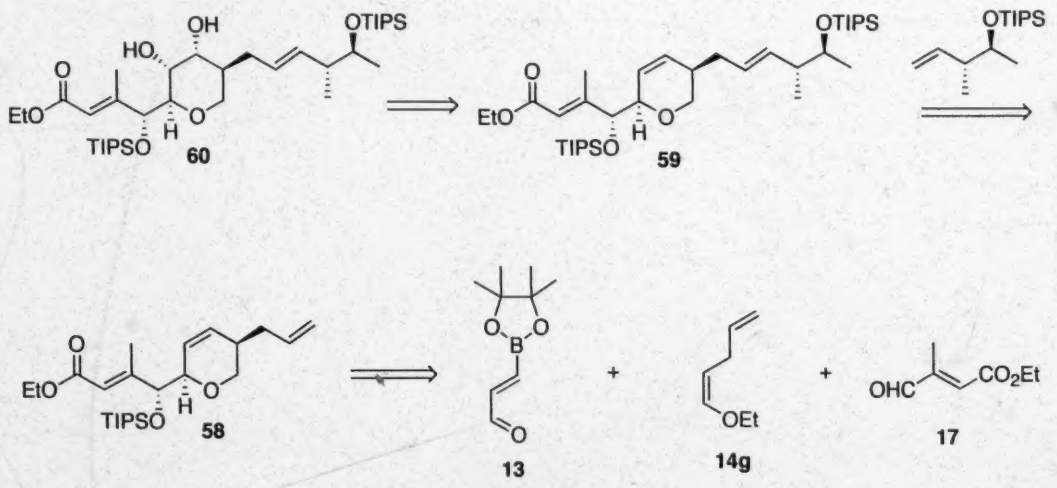
different from that of the natural one. After comparing ^{13}C-NMR of both the synthetic and natural **2** with those of its analogues, we realized that the originally reported ^{13}C-NMR spectrum of natural **2**, said to be recorded in $CDCl_3$, might actually have been recorded in CD_3OD. Indeed, the ^{13}C-NMR spectrum of synthetic **2** in CD_3OD fully matches that of the natural **2** (Table 5-1). Thus, this comparison confirmed that we have successfully completed the first total synthesis of **2**.

Table 5-1. Comparison of the ^{13}C NMR (CD_3OD) spectral data of natural and synthetic product 2

Natural	Synthetic	Natural	Synthetic
176.0	176.0	45.3	45.3
173.0	173.0	43.9	44.0
168.6	168.7	42.8	42.8
161.2	161.2	36.9	37.0
135.7	135.7	33.4	33.4
129.8	129.9	30.1	30.1
116.1	116.2	30.0	30.0
77.5	77.6	29.7	29.8
74.3	74.4	28.8	28.9
72.1	72.1	27.0	27.0
71.8	71.8	26.7	26.7
65.9	66.0	22.3	22.3
65.7	65.7	20.3	20.3
64.8	64.8	16.7	16.7
50.7	50.8	16.3	16.2

5.4.6 Exploiting a cross-metathesis strategy toward the thiomarinols

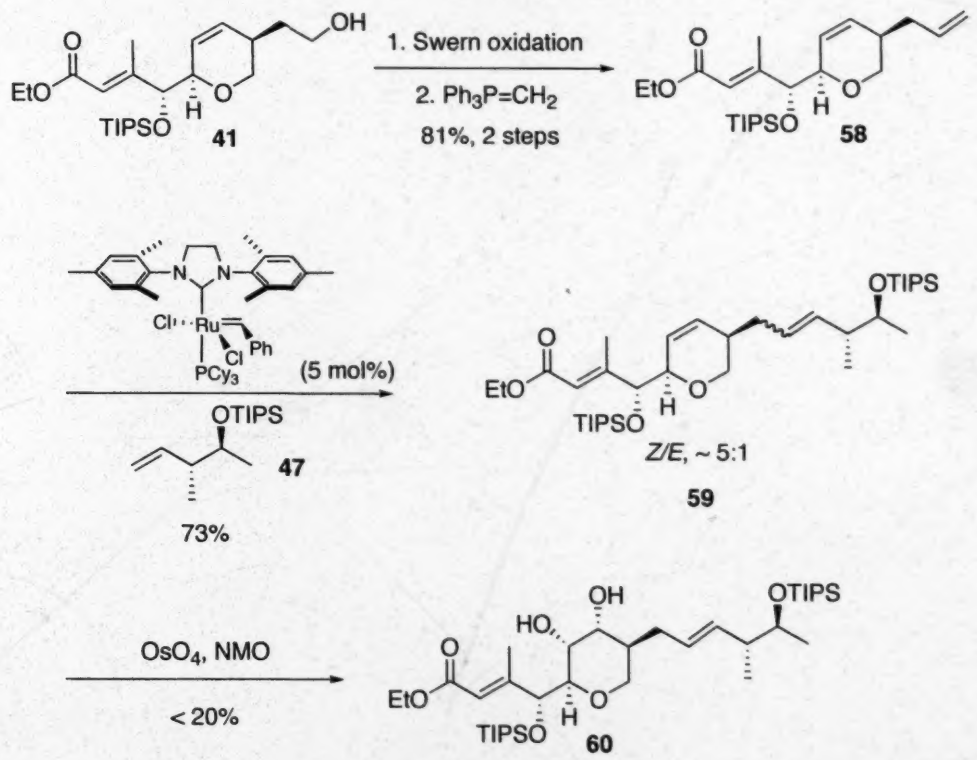
In the total synthesis of **2**, the trans C10-C11 double bond was formed using a Julia-Kocienski coupling. The two coupling partners were prepared *via* several steps from two alkene precursors. We envisioned that the C10-C11 double bond could be constructed by a cross-metathesis approach to furnish intermediate **59** (Scheme 5.21). If the C6-C7 double bond could be selectively dihydroxylated in the presence of the C10-C11 double bond to provide compound **60**, this new strategy would constitute a new route to thiomarinol antibiotics. More importantly, this approach is four steps shorter in the longest linear sequence than the original route, which will greatly facilitate the synthesis of any analogues of the thiomarinols.



Scheme 5.21

To test the cross-metathesis strategy, the known compound **40** was first transformed into **58** *via* Swern oxidation[39] followed by Wittig olefination[40] (Scheme 5.22). Compound **58** was then subjected to the cross-metathesis reaction with

synthon **47** in the presence of 5 mol% of second generation Grubb's catalyst[41] to provide compound **59** as a mixture of C10-C11 *Z/E* double bond isomers. All the attempts at selective dihydroxylation of the C6-C7 olefin, however, failed, because the C10-C11 double bond proved to be more reactive under these conditions. Although the cross-metathesis is not applicable in the synthesis of thiomarinols, this strategy might be used in the synthesis of thiomarinol derivatives containing a C10-C11 epoxide instead of a double bond *via* a hydroxyl-directed epoxidation reaction.[42]



Scheme 5.22

5.4.7. Design and synthesis of simplified thiomarinol derivatives

Having developed a concise route to **2**, our next goal was to synthesize structural analogues in order to discover new derivatives with higher potency and oral bioavailability. It was well known that pseudomonic acid A acted by inhibiting bacterial isoleucyl *t*RNA synthetase. Fortunately, the X-ray crystal structure of pseudomonic acid A bound to bacterial isoleucyl *t*RNA synthetase (Figure 5-8), was reported a few years ago.[43] Inspection of the X-ray structure indicated that the pyran ring and the C8 side arm were essential for binding, whereas the alkoxy side chain of the ester could be modified. This bonding model is in full agreement with SAR studies related to pseudomonic acid A.[3d] Modification of the C12-C14 portion of the molecule led to reduction or complete loss of activity. On the other hand, simplified ester derivatives exhibit similar activity as that of the natural product, with a beneficial reduction of the binding to human serum protein. In addition, analogues with C2-C3 (*Z*) olefin geometry are 100 times less active than pseudomonic acid A. Finally, the studies showed that monic acid A (**1e**) is not biologically active.

Based on the X-ray crystal structure, it was speculated that the additional 4-hydroxyl group in thiomarinols might be able to form hydrogen-bonds with His64 and Asp557 in the bacterial isoleucyl *t*RNA synthetase. Thus, thiomarinols might be stronger inhibitors of bacterial isoleucyl *t*RNA synthetase compared to pseudomonic acids. As a result, they might demonstrate improved antimicrobial activity. The role of the additional 4-hydroxyl group is very intriguing and deserves further investigation.

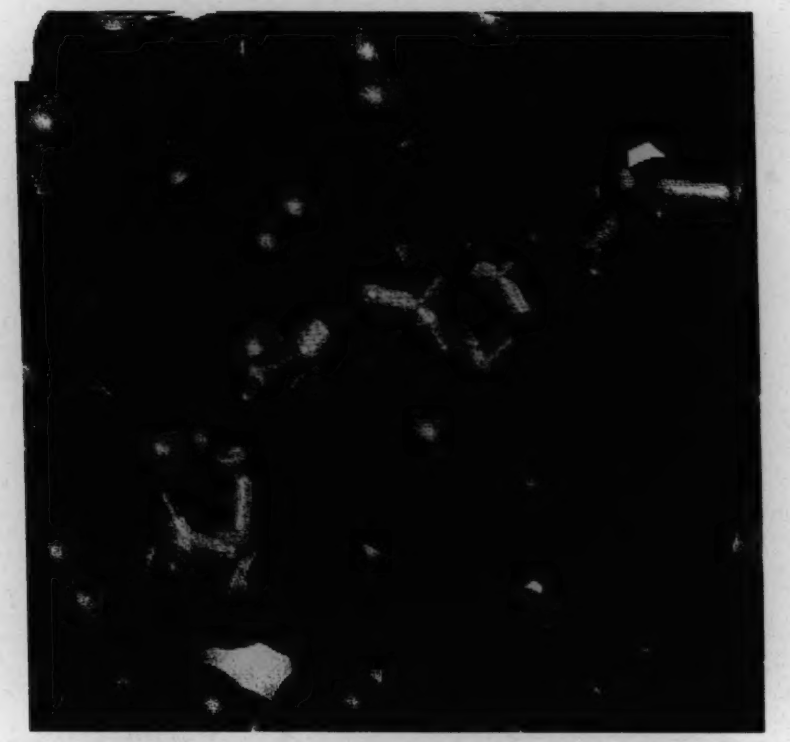
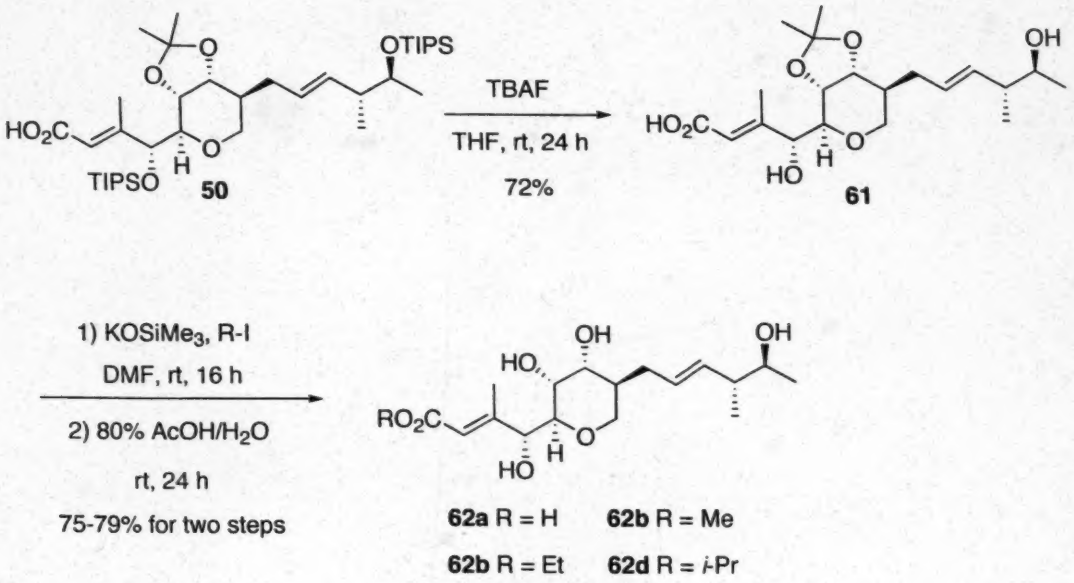


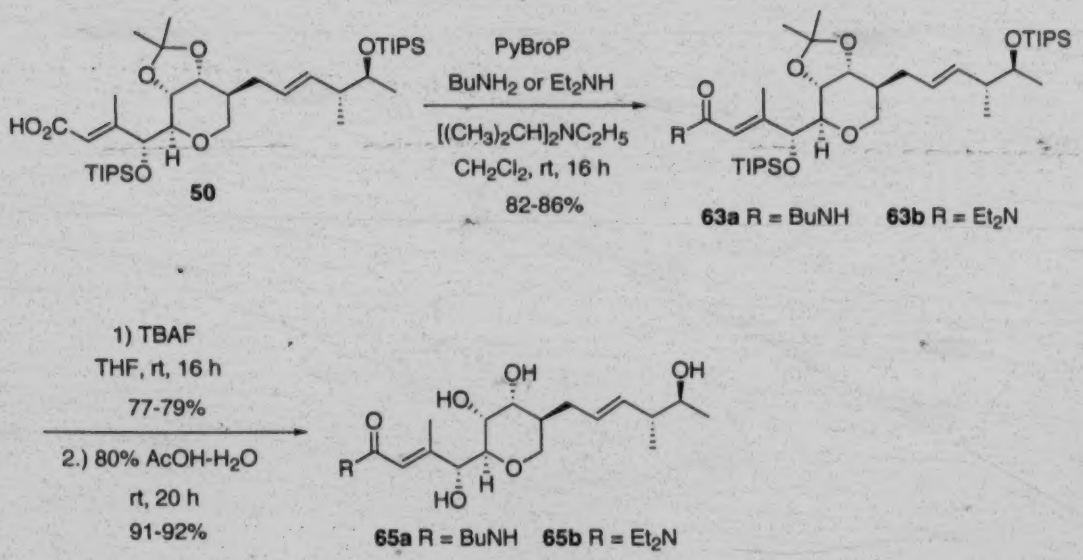
Figure 5-8. X-ray crystal structure of pseudomonic acid A bound to bacterial iso-leucyl tRNA synthetase[43]

In line with the studies of pseudomonic acid A analogues, we set out to make simplified ester analogues to access the role of the lactam unit. The TIPS protecting group in **50** was removed with TBAF in THF to furnish alcohol **61**. The latter was then transformed into **62b**, **62c** and **62d** *via* alkylative esterification followed by deprotection (Scheme 5.23). Methyl, ethyl and isopropyl ester derivatives of **2** were made by the above route. In addition, acid derivative **62a** was synthesized from **61** *via* removal of the ketal protecting group under acidic conditions.



Scheme 5.23

In order to improve the bioavailability of the thiomarinols, the amide analogues, which are believed to be more stable than the ester analogues in vivo, were also designed and synthesized. First, coupling the acid **50** with butylamine or diethylamine in the presence of PyBrop and *N,N*-diisopropylethylamine[44] afforded the amides **63a** and **63b**, respectively (Scheme 5.24). Surprisingly, the use of the more common DIC or DIC/HOBt coupling reagents only gave the desired product in low yield. Subsequent removal of the TIPS and ketal protecting groups under the conditions developed in the synthesis of **2** provided the amide analogues of thiomarinol **65a** and **65b** in good yields.



Scheme 5.24

5.5. The antimicrobial activity of 2 and its simplified analogues.

Compound **2** and its simpler synthetic derivatives were then tested for antimicrobial activity testing against *Staphylococcus aureus* using standard disk diffusion assays (Figure 5-9).[45] Diameter of zones with complete growth inhibition induced by commonly used antibiotics and our compounds were compared. The larger the diameters, the more active the compounds tested.

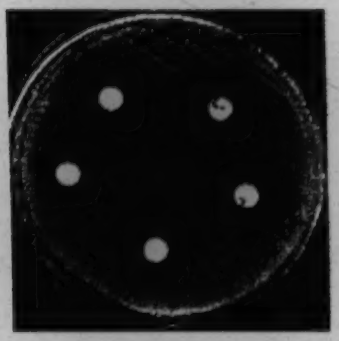


Figure 5-9. Disk diffusion assay against *Staphylococcus aureus*

It was found that synthetic **2** was more active than tetracycline-HCl, but slightly less active than streptomycin, penicillin G and pesudomonic acid A. Amongst the analogues, not surprisingly, the acid derivative **62a** did not show any antimicrobial activity, an outcome similar to monic acid A. While the amide analogues **65a** and **65b** are inferior to the **2** in terms of activity, the simplified ester analogues, especially the ethyl and isopropyl ester **62c** and **62d**, were demonstrated to be more active than **2**. Since the isopropyl ester **62d** is believed to be more stable *in vivo* and less bound to human serum protein than **2** and pseudomonic acid A, it is a promising lead for further development. Although the analogues of thiomarinols exhibit similar antimicrobial activity as that of pseudomonic acid A, it does not necessarily mean that thiomarinols are not binding more tightly to bacterial isoleucyl *t*RNA synthetase because there are other factors such as bioavailabilty that might be the limiting factor (e.g. ability to cross bacterial membrane). To clarify the role of the 4-hydroxyl group in thiomarinols, more studies are required.

Table 5-2. Disk Diffusion Assay against *Staphylococcus aureus*
Diameter of zones with complete growth inhibition (mm)

Antibiotics	ATCC#6538 (mm)	ATCC#25923 (mm)
10μg Streptomycin sulfate (6.86×10^{-3} μmol)	16	14
30μg Tetracycline-HCl (6.02×10^{-2} μmol)	28	29
10 U (6.77 μg) penicillin G sodium (1.9×10^{-2} μmol)	40	32
8.72 μg pseudomonic acid A Ca (1.72×10^{-2} μmol)	32	26
10 μg **2** (1.72×10^{-2} μmol)	16	10
5.917 μg **62a** (1.72×10^{-2} μmol)	No zone	No zone
6.15 μg **62b** (1.72×10^{-2} μmol)	16	13
6.4 μg **62c** (1.72×10^{-2} μmol)	22	21
6.6 μg **62d** (1.72×10^{-2} μmol)	22	21
13.7 μg **65a** (3.436×10^{-2} μmol)	14	Slight
13.7 μg **65b** (3.436×10^{-2} μmol)	15	Slight

5.6 Conclusion

In summary, we have achieved the first total synthesis of a member of the thiomarinol class of marine antibiotics. Compound **2** was synthesized in a remarkable global yield of 22%, over 14 steps from 3-boronoacrolein pinacolate (**13**). The highlight of the synthesis is the efficient catalytic enantio-, regio-, *E*/*Z*-, and diastereoselective inverse electron demand HDA cycloaddition/allylboration sequence. This key operation

provides a rare example of an enantioselective HDA reaction involving acyclic 2-substituted enol ethers. Moreover, the discovery of catalyst-controlled *Z*-enol ether selectivity in the Cr(III)-catalyzed HDA reaction further advanced the existing methodology originally developed by Jacobsen and co-workers. Based on our synthetic route, a number of analogues were also synthesized and some of them demonstrate better antibacterial activities than that of **2**.

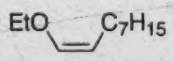
5.7. Experimental

5.7.1 General

The methods described in Section 3.6.1 also apply here.

5.7.2 Experimental procedures

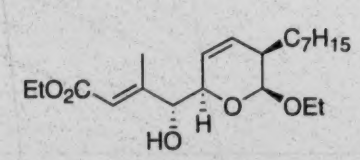
(*Z*)-ethoxy-non-1-ene (14a)



To a solution of sec-BuLi (22.8 mL of a 1.40 M solution in cyclohexane, 32.0 mmol) in THF (40.0 mL) was added dropwise allyl ethyl ether (3.45 g, 40.0 mmol) at –78 °C. After 1 h at –78 °C, 1-iodohexane (5.30 g, 25.0 mmol) was added dropwise and the reaction mixture was stirred for a further 3 h at –78 °C. After warming up to ambient temperature, the reaction was quenched with a saturated aqueous solution of NH_4Cl (40 mL). The resulting mixture was extracted with ether (3 × 70 mL). The extracts were dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and the residue was purified by

flash column chromatography (hexanes) to afford **14a** (3.65 g, 76%). IR (neat film, cm^{-1}) 3031, 1664, 1250, 1185; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (dt, J = 6.3, 1.5 Hz, 1H), 4.33 (dt, J = 6.3, 7.2 Hz 1H), 3.77 (q, J = 7.1 Hz, 2H), 2.02-2.11 (m, 2H), 1.21-1.38 (m, 13H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 107.2, 67.4, 31.9, 29.8, 29.2, 29.2, 23.9, 22.7, 15.2, 14.1; HRMS (EI, *m/z*) calcd for $C_9H_{16}O$ 170.16707, found 170.16703.

(4*R*)-((2*S*,5*R*,6*R*)-6-Ethoxy-5-heptyl-5,6-dihydro-2*H*-pyran-2-yl)-4-hydroxy-3-methyl-but-2*E*-enoyl-oxy-ethane (18a)

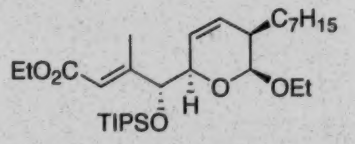


A mixture of 3-boronoacrolein pinacolate (**13**) (0.360 g, 2.00 mmol) and (*Z*)-ethoxy-non-1-ene (**14a**) (0.510 g, 3.00 mmol) was placed in an oven dried 10 mL rbf with a stirbar. To this solution was added **15** (29.0 mg, 0.060 mmol) and powdered BaO (600 mg). After being stirred for 5 h at 20 °C, the reaction mixture was diluted with ether (10 mL), filtered through Celite, and concentrated *in vacuo*. The catalyst was removed through a short column (deactivated silica-gel, hexanes/ether 9:1), and the excess of **14a** was partly recovered by bulb-to-bulb distillation.

A mixture of hetero-Diels-Alder cycloadduct **16a** and ethyl 3-methyl-4-oxocrotonate (**17**) (0.570 g, 4.00 mmol) was stirred at 110 °C for 48 h under argon. After being cooled to ambient temperature, a saturated aqueous solution of $NaHCO_3$ (2 mL) was added to the reaction mixture, which was stirred for 30 min. The resulting mixture

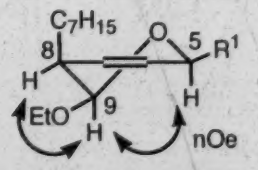
was extracted with ether (2 × 10 mL). The ethereal layers were combined, washed with brine (10 mL), then dried over anhydrous $MgSO_4$. After filtration and concentration *in vacuo* to evaporate ether, ethyl 3-methyl-4-oxocrotonate was partly recovered by bulb-to-bulb distillation. The residue was purified by flash column chromatography (deactivated silica-gel, hexanes/ether 6:1) to afford **18a** (0.545g, 74%). $[\alpha]^{23}_D$ 3.34 (c = 1.0, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3413, 2926, 1717, 1655; ^1H NMR (300 MHz, $CDCl_3$) δ 6.05 (s, 1H), 5.83 (ddd, *J* = 2.9, 2.9, 10.4 Hz, 1H), 5.62 (ddd, *J* = 2.0, 2,0, 10.4 Hz, 1H), 4.72 (d, *J* = 3.7 Hz, 1H), 4.48-4.53 (m, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.97 (dd, *J* = 4.5, 4.5 Hz, 1H), 3.90 (dq, *J* = 11.6, 7.1 Hz, 1H), 3.45-3.53 (m, 2H), 2.22-2.28 (m, 1H), 2.18 (s, 3H), 1.54-1.62 (m, 1H), 1.20-1.42 (m, 17H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 157.0, 129.5, 124.8, 116.8, 98.9, 77.8, 74.3, 65.1, 59.6, 38.1, 31.8, 29.8, 29.7, 29.2, 26.8, 22.6, 15.3, 14.8, 14.3,14.0; HRMS (ESI, *m/z*) calcd for $C_{21}H_{36}O_5Na$ 391.24550, found 391.24535. Assay of enantiomeric excess: Chiral HPLC analysis (Chiralpak AS, 98% hexane/isopropanol, 1.00 mL/min, 210.8 nm), *t*R (major) = 5.384 min., *t*R (minor) = 4.932 min.) 96% ee.

(4*R*)-((2*S*,5*R*,6*R*)-6-Ethoxy-5-heptyl-5,6-dihydro-2*H*-pyran-2-yl)-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoyl-oxy-ethane (21a)



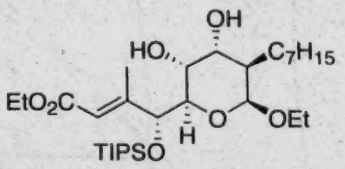
To a solution of (0.263 g, 0.710 mmol) **18a** and 2,6-lutidine (0.214 g, 2.00 mmol) at 0 °C in CH_2Cl_2 (3 mL) was added triisopropyl trifluoromethanesulfonate (0.264 g, 0.860 mmol). The solution was allowed to warm slowly to ambient temperature

overnight. A aqueous saturated $NaHCO_3$ solution (10 mL) was then added and the reaction mixture was stirred for another 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column chromatography (deactivated silica-gel, hexanes) to afford the product (0.328 g, 87%) as a yellow oil. $[\alpha]^{23}_D$ 36.11 (c = 1.5, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 2927, 1720, 1652; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 5.83 (ddd, *J* = 1.9, 5.9, 10.3 Hz, 1H), 5.65 (ddd, *J* = 1.1, 1.1, 10.3 Hz, 1H), 4.58 (d, *J* = 2.8 Hz, 1H), 4.32-4.37 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.88 (dq, *J* = 11.6, 7.1 Hz, 1H), 3.48 (dq, *J* = 11.6, 7.1 Hz, 1H), 2.18 (s, 3H), 2.03-2.08 (m, 1H), 1.63-1.69 (m, 1H), 1.20-1.30 (m, 17H), 1.03-1.12 (m, 21H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 158.0, 130.3, 125.1, 117.4, 100.7, 78.8, 78.7, 64.0, 59.5, 39.2, 31.9, 30.0, 29.3, 28.8, 27.0, 22.7, 18.0, 16.7, 15.2, 14.3, 14.1, 12.2; HRMS (ESI, *m/z*) calcd for $C_{30}H_{56}O_5SiNa$ 547.37892, found 547.37855.



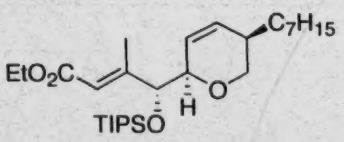
TROESY experiments indicated that the relative stereochemistry around the six-membered ring is *cis*. Nuclear Over-hauser enhancement were observed between 9-H (4.58 ppm) and 8-H (2.03-2.18 ppm), and between 9-H and 5-H (4.32-4.37 ppm).

(4*R*)-((2*S*,3*R*,4*R*,5*R*,6*R*)-6-Ethoxy-5-heptyl-3,4-dihydroxy-tetrahydro-pyran-2-yl)-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoyl-oxy-ethane (22a)



Dihydropyran **21a** (0.062 g, 0.120 mmol) was dissolved in acetone/water (1 mL, 9:1). Then, the monohydrate of *N*-methylmorpholine *N*-oxide (0.020 g, 0.180 mmol) and osmium tetroxide (2.5 wt% solution in 2-methyl-2-propanol, 0.120 mL, 0.010 mmol) were added and the mixture was stirred at ambient temperature overnight. It was then diluted with a saturated aqueous solution of sodium sulfite (5 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes/EtOAc, 1:1) to afford the title compound (0.078 g, 73%) as a yellow oil. $[\alpha]^{23}_D$ -94.24 (c = 1.0, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3486, 2927, 1720, 1657; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58-7.72 (m, 5H), 6.02 (s, 1H), 4.86 (d, *J* = 2.3 Hz, 1H), 4.56 (d, *J* = 3.9 Hz, 1H), 3.95-3.99 (m, 1H), 3.91 (dd, *J* = 3.9, 9.8 Hz, 1H), 3.82 (dq, *J* = 9.7, 7.1 Hz, 1H), 3.72 (dd, *J* = 3.3, 9.7 Hz, 1H), 3.58 (s, 1H), 3.51 (dq, *J* = 9.7, 7.1 Hz, 1H), 2.62 (s, 1H), 2.12 (s, 3H), 1.92-1.98 (m, 1H), 1.61-1.68 (m, 1H), 1.01-1.32 (m, 38H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 157.1, 117.1, 100.3, 78.1, 74.4, 70.6, 66.0, 64.7, 59.7, 44.1, 31.8, 29.7, 29.1, 28.2, 23.7, 22.6, 17.9, 17.5, 15.2, 14.3, 14.1, 12.1; HRMS (ESI, *m/z*) calcd for $C_{30}H_{58}O_7SiNa$ 581.38440, found 581.38442.

(4*R*)-((2*S*,5*R*)-5-Heptyl-5,6-dihydro-2*H*-pyran-2-yl)-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoyl-oxy-ethane (23a)

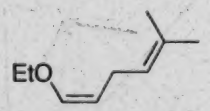


To a solution of **21a** (0.099 g, 0.190 mmol) and triethylsilane (0.120 g, 1.00 mmol) in CH_2Cl_2 (2.5 mL) was added $TiCl_4$ (0.200 mL, 1.00 M solution in CH_2Cl_2, 0.200 mmol) dropwise at –50 °C. After being stirred for 2.5 h at –50 °C, the reaction mixture was allowed to warm up to ambient temperature and quenched with an aqueous saturated $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes/EtOAc 95:5) to afford the title compound (0.078 g, 86%) as a yellow oil. $[\alpha]^{23}_D$ 28.46 (c = 1.0, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 2926, 1719, 1652, 1464; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83-5.91 (m, 2H), 5.68 (ddd, *J* = 1.6, 1.6, 10.4 Hz, 1H), 4.31 (d, *J* = 5.6 Hz, 1H), 4.19-4.23 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.60-3.70 (m, 2H), 2.08 (s, 3H), 1.90-1.98 (m, 1H), 1.21-1.38 (m, 15H), 1.00-1.10 (m, 21H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 158.1, 130.9, 125.2, 117.4, 78.8, 76.7, 67.3, 59.5, 34.7, 33.3, 31.9, 29.7, 29.2, 27.2, 22.6, 18.0, 16.5, 14.3, 14.1, 12.3; HRMS (ESI, *m/z*) calcd for $C_{28}H_{52}O_4SiNa$ 503.35271, found 503.35270.

1-Ethoxy-5, 5-dimethyl-pent-4-ene-1-yne (33)

To a solution of ethoxyacetylene (3.50 g, 50.0 mmol) in THF (70 mL) was added dropwise n-BuLi (38.0 mL of a 1.48 M solution in hexanes, 55.0 mmol) at –78 °C. After one hour at –78 °C, HMPA (20.0 mL, 115 mmol) was added dropwise while the temperature was maintained at –78 °C. The reaction mixture was stirred for a further 30 min. 1-Bromo-3-methylbut-2-ene (6.80 g, 45.0 mmol) was added and the solution was allowed to warm up to ambient temperature. After stirred overnight, the reaction was quenched with water (60 mL). The resulting mixture was extracted with ether (3 × 100 mL). The extracts were dried over anhydrous $MgSO_4$, concentrated *in vacuo* and the residue was purified by distillation (b.p. 40 °C, 1 mm Hg) to give the title compound (5.72 g, 92%) as a colorless liquid. IR ($CHCl_3$, cast, cm^{-1}) 2251, 1262; ^1H NMR (400 MHz, $CDCl_3$) δ 5.17 (tq, J = 6.9, 1.1 Hz 1H), 4.02 (q, J = 7.0 Hz, 2H), 2.82(d, J = 6.9 Hz, 2H), 1.66 (d, J = 1.1 Hz 3H), 1.62 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.5, 121.0, 88.9, 73.8, 36.3, 25.5, 17.5, 16.2, 14.3; HRMS (EI, *m/z*) calcd for $C_9H_{14}O$ 138.10466, found 138.10483.

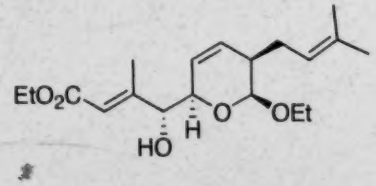
(1*Z*)-1-Ethoxy-5,5-dimethyl-pent-1,4-diene (14d)



The acetylenic ether **33** (3.10 g, 22.4 mmol) was dissolved in ethyl acetate-pyridine (10:1, v/v, 44 mL), and Lindlar catalyst (360 mg) was added. The reaction was fitted with a three-way stopcock, and a hydrogen-filled balloon was attached. The remaining inlet was attached to vacuum (20 mm Hg), and the reaction vessel was carefully evacuated until the solvent just began to boil. The reaction vessel then filled

with hydrogen gas from the balloon. This operation was repeated twice. The reaction was then allowed to stir under an excess of hydrogen gas. After 16 h, the reaction was filtered through a plug of Celite, and the Celite was washed with ether (60 mL). The mixture was washed with water (2 × 40 mL), aqueous saturated $KHSO_4$ solution (2 × 40 mL) and brine (2 × 40 mL). The extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give the crude title compound (2.98 g, 95%) as a colorless liquid. IR (neat film, cm^{-1}) 3036, 2977, 1660, 1443; ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (dt, J = 6.2, 1.6 Hz, 1H), 5.12 (tq, J = 7.3, 1.1 Hz 1H), 4.32 (dt, J = 6.2, 7.4 Hz 1H), 3.78 (q, J = 7.0 Hz, 2H), 2.78 (ddd, J = 7.4, 7.3, 1.6 Hz, 2H), 1.69 (d, J = 1.1 Hz, 3H), 1.63 (s, 3H); 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 131.4, 123.3, 105.8, 67.5, 25.6, 23.0, 17.5, 15.2; HRMS (EI, *m/z*) calcd for $C_9H_{16}O$ 140.12012, found 140.12041.

(4*R*)-((2*S*,5*R*,6*R*)-6-Ethoxy-5-(3-methyl-but-2-enyl)-5,6-dihydro-2*H*-pyran-2-yl)-4-hydroxy-3-methyl-but-2*E*-enoyl-oxy-ethane (18d)

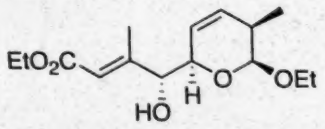


A mixture of 3-boronoacrolein pinacolate (**13**) (2.73 g, 15.0 mmol) and enol ether **14d** (3.15 g, 22.5 mmol) was placed in an oven dried 50 mL rbf with a stirbar. To this solution was added **15** (220 mg, 0.450 mmol) and powdered BaO (4.00 g). After being stirred at 20 °C for 5 h, the reaction mixture was diluted with ether (50 mL), filtered through Celite, concentrated *in vacuo*. The catalyst was removed through a short column

(deactivated silica-gel, hexanes/ether 9:1), and the excess of enol ether **14d** was partly recovered by bulb-to-bulb distillation.

A mixture of hetero-Diels-Alder cycloadduct **16d** and ethyl 3-methyl-4-oxocrotonate (**17**) (4.00 g, 28.0 mmol) was stirred at 110 °C for 48 h under argon. After being cooled to ambient temperature, a saturated aqueous $NaHCO_3$ solution (20 mL) was added to the reaction mixture, which was stirred for 30 min. The resulting mixture was extracted with ether (2 × 60 mL). The ethereal layers were combined, washed with brine (50 mL), then dried over anhydrous $MgSO_4$. After filtration and concentration *in vacuo* to evaporate ether, aldehyde **17** was partly recovered by bulb-to-bulb distillation. The residue was purified by flash column chromatography (deactivated silica-gel, hexanes/ether 6:1) to afford (3.85 g, 76%) of **18d** as yellow oil. $[\alpha]^{23}_D$ –19.9 (c = 1.7, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3412, 3036, 1715, 1651; ^1H NMR (300 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.80 (ddd, *J* = 2.7, 2.7, 10.4 Hz, 1H), 5.62 (ddd, *J* = 2.1, 2.1, 10.4 Hz, 1H), 5.15 (tq, *J* = 7.4, 1.1 Hz, 1H), 4.72 (d, *J* = 3.6 Hz, 1H), 4.51-4.56 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.96-4.02 (m, 1H), 3.88 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.56-3.63 (m, 1H), 3.46 (dq, *J* = 9.5, 7.1 Hz, 1H), 2.20-2.35 (m, 2H), 2.18 (d, 3H), 2.02-2.12 (m, 1H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.62 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 157.2, 133.3, 129.1, 125.0, 121.6, 116.6, 98.5, 77.7, 74.1, 65.1, 59.5, 38.5, 28.4, 25.7,17.8, 15.3, 14.8, 14.2; HRMS (ESI, *m/z*) calcd for $C_{19}H_{30}O_5Na$ 361.199094, found 361.198919. Assay of enantiomeric excess: Chiral HPLC analysis (Chiralpak AS, 98% hexane/isopropanol, 1.00 mL/min, 210.8 nm), *t*R (major) = 6.523 min., *t*R (minor) = 5.912 min.) 96% ee.

(4*R*)-((2*S*,5*R*,6*R*)-6-Ethoxy-5-methyl-5,6-dihydro-2*H*-pyran-2-yl)-4-hydroxy-3-methyl-but-2*E*-enoyl-oxy-ethane (36a)

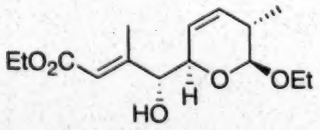


A mixture of 3-boronoacrolein pinacolate (**13**) (0.182 g, 1.00 mmol) and ethyl 1-propenyl ether (**34**) (*Z*/*E* 3:1) (0.170 g, 2.00 mmol) was placed in an oven dried 10 mL rbf with a stirbar. To this solution was added **15** (15.0 mg, 0.030 mmol) and powdered BaO (0.300 g). After being stirred for 14 h at 20 °C (^{1}H-NMR spectroscopy showed that the ratio of ethyl (*Z*)-1-propenyl ether and ethyl (*E*)-1-propenyl ether in the flask was about 1:1 after completion of the cycloaddition). The reaction mixture was diluted with ether (5 mL), filtered through Celite, and concentrated *in vacuo*. The catalyst was removed through a short column (deactivated silica-gel, hexanes/ether 9:1) to afford the cycloadduct **35a** and **35b** (^{1}H-NMR spectroscopy showed that the ratio of two cycloadducts was about 96:4).

A mixture of hetero-Diels-Alder cycloadduct **35a** and **35b** and ethyl 3-methyl-4-oxocrotonate (**17**) (0.280 g, 2.00 mmol) was stirred at 110 °C for 48 h under argon. After being cooled to ambient temperature, an aqueous saturated $NaHCO_3$ solution (2 mL) was added to the reaction mixture, which was stirred for 30 min. The resulting mixture was extracted with ether (2 × 10 mL). The ethereal layers were combined, washed with brine (10 mL), then dried over anhydrous $MgSO_4$. After filtration and concentration *in vacuo* to evaporate ether, ethyl 3-methyl-4-oxocrotonate was partly recovered by bulb-to-bulb distillation. The residue was purified by flash column chromatography (deactivated

silica-gel, hexanes/ether 6:1) to afford allylboration product of **36a** (0.213 g, 75%). $[\alpha]^{23}_{D}$ 19.2 (c = 2.8, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3410, 2978, 1716, 1653; ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (s, 1H), 5.79 (ddd, *J* = 2.5, 3.8, 10.3 Hz, 1H), 5.58 (ddd, *J* = 1.9, 1.9, 10.3 Hz, 1H), 4.69 (d, *J* = 3.6 Hz, 1H), 4.44-4.49 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.94-4.02 (m, 1H), 3.90 (dq, *J* = 9.7, 7.1 Hz, 1H), 3.52 (dq, *J* = 9.7, 7.1 Hz, 1H), 3.35-3.42 (m, 1H), 2.30-2.43 (m, 1H), 2.20 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 156.8, 131.2, 124.7, 117.0, 99.4, 77.9, 74.6, 65.0, 59.6, 33.2, 15.3, 14.9, 14.3,14.3; HRMS (ESI, *m/z*) calcd for $C_{15}H_{24}O_5Na$ 307.15159, found 307.15132. Assay of enantiomeric excess: Chiral HPLC analysis (Chiralpak AS, 100% hexanes, 1.00 mL/min, 210.8 nm), *t*R (major) = 10.113 min., *t*R (minor) = 9.546 min.) 96% ee.

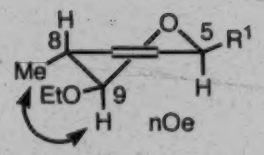
4-(6-Ethoxy-5-methyl-5,6-dihydro-2*H*-pyran-2-yl)-4-hydroxy-3-methyl-but-2*E*-enoyl-oxy-ethane (36b)



A mixture of 3-boronoacrolein pinacolate (**13**) (0.182 g, 1.00 mmol) and ethyl 1-propenyl ether (**34**) (*Z*/*E* 3:1) (0.170 g, 2.0 mmol) was placed in an oven dried 10 mL RBF with a stirbar. To this solution was added $Yb(fod)_3$ (106 mg, 0.100 mmol). After being stirred for 14 h at 20 °C (^1H-NMR spectroscopy showed that the ratio of ethyl (*Z*)-1-propenyl ether and ethyl (*E*)-1-propenyl ether in the flask was about 3:1 after the completion of the reaction). The reaction mixture was diluted with ether (5 mL), filtered through Celite, and concentrated *in vacuo*. The catalyst was removed through a short

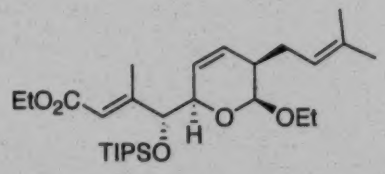
column (deactivated silica-gel, hexanes/ether 9:1) to afford the cycloadduct **35a** and **35b** (^{1}H-NMR spectroscopy showed that the ratio of two cycloadducts was about 3:1).

A mixture of hetero-Diels-Alder cycloadduct **35a** and **35b** and ethyl 3-methyl-4-oxocrotonate **17** (0.280 g, 2.00 mmol) was stirred at 110 °C for 48 h under argon. After being cooled to ambient temperature, an aqueous saturated $NaHCO_3$ solution (2 mL) was added to the reaction mixture, which was stirred for 30 min. The resulting mixture was extracted with ether (2 × 10 mL). The ethereal layers were combined, washed with brine (10 mL), then dried over anhydrous $MgSO_4$. After filtration and concentration *in vacuo* to evaporate ether, ethyl 3-methyl-4-oxocrotonate was partly recovered by bulb-to-bulb distillation. The residue was purified by flash column chromatography (deactivated silica-gel, hexanes/ether 6:1) to afford allylboration product of **36a** (0.159 g, 56%) whose spectroscopic data are in full agreement with its enantioenriched compound, and allylboration product of **36b** (0.0540 mg, 19%) whose stereochemistry was partly confirmed by nOe study. IR ($CHCl_3$, cast, cm^{-1}) 3472, 3034, 1716, 1653; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.72 (ddd, J = 2.4, 2.8, 10.3 Hz, 1H), 5.56 (ddd, J = 1.9, 1.9, 10.3 Hz, 1H), 4.37-4.42 (m, 1H), 4.33 (d, J = 6.0 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.99 (d, J = 4.5 Hz, 1H), 3.90 (dq, J = 9.6, 7.1 Hz, 1H), 3.52 (dq, J = 9.6, 7.1 Hz, 1H), 3.10 (brs, 1H), 2.22-2.36 (m, 1H), 2.20 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.02 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 156.4, 131.7, 124.6, 117.5, 103.5, 78.1, 75.0, 64.9, 59.8, 34.8, 16.8, 15.4, 15.2, 14.4. HRMS (ESI, *m/z*) calcd for $C_{15}H_{24}O_5Na$ 307.15159, found 307.15136.



Nuclear Over-hauser enhancement were observed between 9-H (4.33 ppm) and methyl group (1.02 ppm).

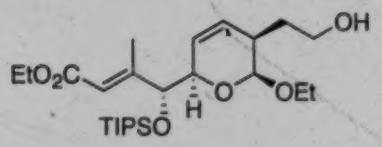
(4*R*)-[(2*S*,5*R*,6*R*)-6-Ethoxy-5-(3-methyl-but-2-enyl)-5,6-dihydro-2*H*-pyran-2-yl]-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoyl-oxy-ethane (21d)



To a solution of **18d** (7.46 g, 22.1 mmol) and 2,6-lutidine (7.00 g, 65.0 mmol) at 0 °C in CH_2Cl_2 (85 mL) was added triisopropyl trifluoromethanesulfonate (8.12 g, 26.5 mmol). The solution was allowed slowly warmed to ambient temperature overnight. An aqueous saturated $NaHCO_3$ solution (50 mL) was then added and the reaction mixture was stirred for another 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column chromatography (deactivated silica-gel, hexanes) to afford the title compound (10.2 g, 93%) as a yellow oil. $[\alpha]^{23}_D$ 11.21 (c = 1.5, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 2943, 1719, 1652; ^1H NMR (500MHz, $CDCl_3$) δ 5.90 (s, 1H), 5.79 (ddd, *J* = 1.8, 5.7, 10.3 Hz, 1H), 5.65 (ddd, *J* = 1.0, 1.0, 10.3 Hz, 1H), 5.15 (tq, *J* = 7.4, 1.1 Hz, 1H), 4.62 (d, *J* = 2.9 Hz, 1H), 4.33-4.39 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.90 (dq, *J* = 9.6, 7.2 Hz, 1H), 3.52 (dq, *J* = 9.6, 7.2 Hz, 1H), 2.33-2.41 (m, 1H), 2.18 (s, 3H), 2.05-2.12 (m, 1H), 1.87-2.12

(m, 1H), 1,68 (s, 3H), 1.53 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.22 (t, J=7.1 Hz, 3H), 1.03-1.12 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 158.0, 132.3, 130.4, 124.9, 122.4, 117.4, 100.6, 79.0, 78.5, 64.0, 59.6, 39.7, 27.6, 25.8, 18.0, 16.8, 15.2, 14.3, 12.3; HRMS (ESI, *m/z*) calcd for $C_{28}H_{50}O_5SiNa$ 517.33198, found: 517.33202.

(4*R*)-[(2*S*,5*R*,6*R*)-6-Ethoxy-5-(2-hydroxy-ethyl)-5,6-dihydro-2*H*-pyran-2-yl]-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoyl-oxy-ethane (40)

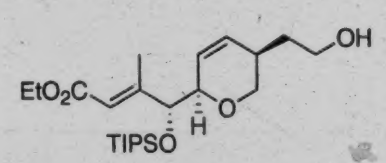


A heterogeneous mixture of potassium carbonate (9.00 g, 65.0 mmol), potassium ferricyanide (14.4 g, 43.6 mmol), $(DHDQ)_2PHAL$ (385 mg, 0.494 mmol), 2.5% osmium tetroxide in 2-methyl-2-propanol (5.25 mL, 4.19 mmol), methanesulfonamide (2.07 g, 21.7 mmol), and compound **21d** (10.7 g, 21.7 mmol) in *tert*-butyl alcohol (125 mL) and water (125 mL) was stirred at 0 °C for 2 h. The mixture was then diluted with an saturated aqueous solution of sodium sulfite (50 mL) and extracted with ether (2 × 200 mL). The combined organic layers were concentrated to afford crude **38**.

Compound **38** was diluted with THF (40 mL) and water (40 mL) followed by addition of sodium periodate (7.00 g, 33.0 mmol) portionwise. After stirring at ambient temperature for 1h, the solution was diluted with aqueous sodium sulfite (50 mL) and extracted with ether (2 × 200 mL), and the combined organic layers were concentrated to provide crude **39**.

To the solution of crude aldehyde **39** in ethanol (90 mL) was added portionwise sodium borohydride (1.64 g, 43.4 mmol), and the mixture was stirred for 30 min. An aqueous saturated $NaHCO_3$ solution (50 mL) was then added, and the mixture was extracted with ether (2 × 200 mL). The organic layers were collected, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (deactivated silica-gel, hexanes/EtOAc 85:15) to afford **40** (8.98 g, 88%) as yellow oil. $[\alpha]^{23}_D$ 60.16 (c = 1.9, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3419, 2943, 1718, 1652; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (s, 1H), 5.80 (ddd, *J* = 1.9, 5.8, 10.1 Hz, 1H), 5.66 (ddd, *J* = 1.2, 1.2, 10.1 Hz, 1H), 4.65 (d, *J* = 2.9 Hz, 1H), 4.31-4.39 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.96 (dq, *J* = 9.5, 7.1 Hz, 1H), 3.63-3.73 (m, 1H), 3.50-3.62 (m, 2H), 2.23-2.33 (m, 1H), 2.16 (s, 3H), 1.78-1.92 (m, 1H), 1.52-1.63 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.00-1.10 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 157.4, 129.9, 125.3, 117.7, 100.3, 79.0, 78.6, 64.3, 61.4, 59.6, 37.9, 32.0, 17.9, 17.9, 16.5, 15.0, 14.3, 12.2; HRMS (ESI, *m/z*) calcd for $C_{25}H_{46}O_6SiNa$ 493.29559, found 493.29566.

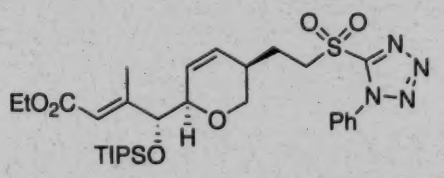
(4*R*)-[(2*S*,5*R*)-5-(2-Hydroxy-ethyl)-5,6-dihydro-2*H*-pyran-2-yl]-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoyl-oxy-ethane (41)



To a solution of **40** (7.64 g, 16.3 mmol) and triethylsilane (9.30 g, 80.0 mmol) in CH_2Cl_2 (120 mL) was added $TiCl_4$ (19.5 mL, 1.00 M solution in CH_2Cl_2, 19.5 mmol) dropwise at –50 °C. After being stirred for 2.5 h at –50 °C, the reaction mixture was

allowed to warm up to ambient temperature and quenched with an aqueous saturated $NaHCO_3$ solution (60 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes/EtOAc 4:1) to afford the title compound (5.88 g, 85%) as yellow oil. $[\alpha]^{23}_D$ 24.44 (c = 1.4, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3466, 2944, 1718, 1651, 1463; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78-5.92 (m, 3H), 4.33 (d, *J* = 5.6 Hz, 1H), 4.21-4.26 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.60-3.82 (m, 4H), 2.15-2.23 (m, 1H), 2.12 (s, 3H), 1.60-1.70 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.00-1.10 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 157.7, 129.8, 126.4, 117.7, 78.7, 77.7, 68.0, 60.1, 59.7, 36.3, 31.8, 18.0, 16.5, 14.3, 12.3; HRMS (ESI, *m/z*) calcd for $C_{23}H_{42}O_5SiNa$ 449.269923, found 449.269854.

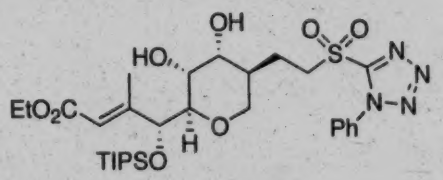
(4*R*)-{(2*S*,5*R*)-5-[2-(1-Phenyl-1*H*-tetrazole-5-sulfonyl)-ethyl]-tetrahydro-pyran-2-yl}-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoyl-oxy-ethane (42)



Triphenylphosphine (4.28 g, 16.3 mmol), 1-phenyl-1-1*H*-tetrazole-5-thiol (2.90 g, 16.3 mmol), and the above alcohol **41** (5.80 g 13.6 mmol) were dissolved in THF (110 mL). To this solution was added DIAD (3.30 g, 16.3 mmol) at ambient temperature. After stirring for 4 h, the reaction was diluted with EtOH (200 mL) and cooled to 0 °C. In a separate flask were mixed 30% aqueous H_2O_2 (23.0 mL, 203 mmol) and ammonium molybdate tetrahydrate (5.47 g, 20.4 mmol), producing a bright yellow solution that was

added by syringe to the reaction flask. After stirring overnight at ambient temperature, the reaction was diluted by the addition of water (200 mL) and ether (200 mL). The layers were separated and the aqueous layer was extracted with ether (2 × 200 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column chromatography (hexanes/EtOAc, 10:1) to afford **42** (7.65 g, 91%) as yellow oil. $[\alpha]^{23}_D$ 4.33 (c = 3.4, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 2944, 1713, 1652, 1497; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58-7.72 (m, 5H), 5.81-5.96 (m, 3H), 4.33 (d, *J* = 5.8 Hz, 1H), 4.21-4.27 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.65-3.87 (m, 4H), 2.20-2.28 (m, 1H), 2.10 (s, 3H), 2.03-2.09 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.00-1.10 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 157.1, 153.4, 133.1, 131.3, 129.6, 128.4, 127.7, 125.1, 118.1, 78.3, 77.8, 67.4, 59.7, 53.7, 32.7, 25.8, 18.0, 17.9, 16.7, 14.2, 12.2; HRMS (ESI, *m/z*) calcd for $C_{30}H_{46}N_4O_6SiSNa$ 641.27996, found 641.27991.

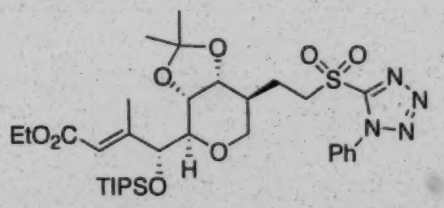
(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-Dihydroxy-5-[2-(1-Phenyl-1*H*-tetrazole-5-sulfonyl)-ethyl]-tetrahydro-pyran-2-yl}-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoyl-oxy-ethane (43)



Dihydropyran **42** (7.65 g, 11.7 mmol) was dissolved in acetone/water (120 mL, 9:1). Then, the monohydrate of *N*-methylmorpholine *N*-oxide (2.06 g, 17.6 mmol) and osmium tetroxide (2.5 wt% solution in 2-methyl-2-propanol, 11.5 mL, 0.920 mmol) were

added and the mixture was stirred at ambient temperature overnight. It was then diluted with aqueous sodium sulfite (50 mL) and extracted with EtOAc (2 × 200 mL). The combined organic layers was washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes/EtOAc, 1:1) to afford the title compound **43** (7.04 g, 87%) as yellow oil. $[\alpha]^{23}_D$ 38.13 (c = 2.6, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3481, 2943, 1712, 1652; ^1H NMR (300 MHz, $CDCl_3$-D_2O) δ 7.58-7.72 (m, 5H), 6.02 (s, 1H), 4.56 (d, *J* = 3.9 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.88-3.95 (m, 2H), 3.73-3.83 (m, 4H), 3.68 (dd, *J* = 3.3, 9.7 Hz, 1H), 3.58 (d, *J* = 11.8 Hz, 1H), 2.10 (s, 3H), 1.90-2.12 (m, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.00-1.08 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 156.2, 153.2, 132.9, 131.4, 129.7, 125.0, 117.6, 78.2, 76.8, 69.3, 66.3, 64.8, 59.9, 54.3, 39.2, 21.7, 18.0, 18.0, 17.5, 14.4, 12.2; HRMS (ESI, *m/z*) calcd for $C_{30}H_{49}N_4O_8SiS$ 653.30349, found 653.30317.

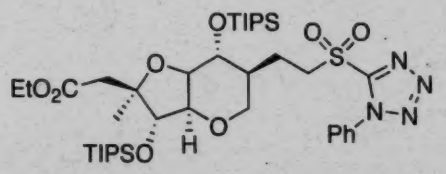
(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-O-Isopropylidene-3,4-dihydroxy-5-[2-(1-Phenyl-1*H*-tetrazole-5-sulfonyl)-ethyl]-tetrahydro-pyran-2-yl}-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoyl-oxy-ethane (44)



To a stirred suspension of diol **43** (5.63 g, 8.63 mmol) in EtOAc (12 mL) and anhydrous $MgSO_4$ was added 2,2-dimethoxypropane (12 mL) and a few crystals of *p*-toluenesulfonic acid monohydrate. After being stirred at ambient temperature for one

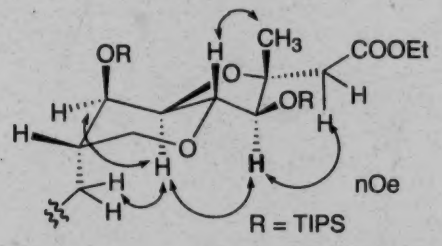
hour, the solution was diluted with EtOAc (50 mL) and anhydrous $MgSO_4$ was removed via filtration. The resulting solution was washed with an aqueous saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated to afford **44** (6.11 g, 98%) as yellow oil. $[\alpha]^{23}_D$ –4.32 (c = 0.63, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 2942, 1715, 1652; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58-7.72 (m, 5H), 5.88 (s, 1H), 4.06-4.22 (m, 4H), 4.00 (dd, *J* = 5.6, 8.4 Hz, 1H), 3.45-3.98 (m, 4H), 3.36 (dd, *J* = 4.5, 8.4 Hz, 1H), 2.16 (s, 3H), 2.05-2.15 (m, 3H), 1.46 (s, 3H), 1.31 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.00-1.08 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 157.9, 153.3, 133.0, 131.5, 129.7, 125.0, 117.3, 109.0, 80.1, 78.8, 75.8, 70.8, 65.6, 59.6, 54.2, 35.8, 28.1, 26.2, 23.4, 18.0, 18.0, 15.9, 14.3, 12.6; HRMS (ESI, *m/z*) calcd for $C_{33}H_{52}N_4O_8SiSNa$ 715.31674, found 715.31668.

[(2*R*)-Methyl-(2*R*,3*S*,6*S*,7*R*)-[2--(1-Phenyl-1*H*-tetrazole-5-sulfonyl)-ethyl]-3,7-(bistriisopropylsilyoxyl)-hexahydro-furo[3.2-β]pyran-2-yl]-acetic acid ethyl ester (45)



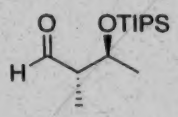
To a solution of above diol **43** (66.0 mg, 0.100 mmol) and 2,6-lutidine (107 mg, 1.00 mmol) at 0 °C in CH_2Cl_2 (0.5 mL) was added triisopropyl trifluoromethanesulfonate (153 mg, 0.500 mmol). The solution was allowed to slowly warm up to ambient temperature overnight. An aqueous saturated aqueous $NaHCO_3$ solution (2 mL) was then added and the reaction mixture was stirred for another 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic

layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes/ EtOAc 95: 5) to afford the bicyclic compound (71.0 mg, 88%). $[\alpha]^{23}_D$ 20.68 (c = 1.0, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 2943, 1733, 1498; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58-7.72 (m, 5H), 4.41 (d, *J* = 8.4 Hz, 1H), 4.19-4.23 (m, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.87 (dd, *J* = 2.6, 12.0 Hz, 1H), 3.71-3.82 (m, 3H), 3.64 (d, *J* = 12.0 Hz, 1H), 3.48 (dd, *J* = 2.2, 10.1 Hz, 1H), 2.60 (ABq, *J* = 13.5 Hz, 1H), 2.55 (ABq, *J* = 13.5 Hz, 1H), 2.07-2.22 (m, 1H), 1.91-2.05 (m, 1H), 1.73-1.82 (m, 1H), 1.22-1.68 (m, 6H), 1.00-1.09 (m, 42H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 153.3, 133.0, 131.5, 129.7, 125.0, 82.4, 78.8, 78.5, 73.0, 69.8, 65.6, 60.3, 54.7, 45.2, 42.8, 23.7, 33.6, 18.1, 18.0, 17.9, 14.2, 12.4, 12.2; HRMS (ESI, *m/z*) calcd for $C_{39}H_{68}N_4O_8Si_2SNa$ 831.41887, found 831.41889.



TROESY experiments indicated that the rigid bicyclic compound **45** had the same relative stereochemistry as the analogues made from thiomarinol.[4a, 4d] Nuclear Overhauser enhancements were observed between 4-H (4.41 ppm) and 2-H (2.60, 2.55 ppm), and between 4-H and 6-H (3.48 ppm), and between 6-H and 7-H (4.19-4.23 ppm), and between 6-H and 9-H (2.07-2.22, 1.91-2.05 ppm), and between 5-H (3.71-3.82 ppm) and 11-H (1.06 ppm). This result confirmed that the structure of the hetero [4+2]/allylboration product was as we described in the chapter.

(2*S*, 3*S*)-3-triisopropylsilyloxy-2-methylbutanal (44)

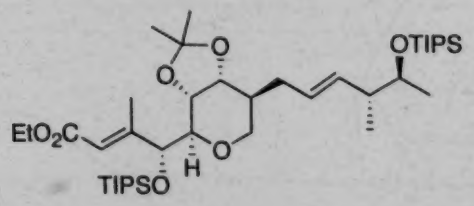


To a solution of (2*S*, 3*R*)-3-methyl-4-penten-2-ol (**46**)(1.80 g, 18.0 mmol) and 2,6-lutidine (5.70 g, 53.0 mmol) at 0 °C in CH_2Cl_2 (60 mL) was added triisopropyl trifluoromethanesulfonate (6.07 g, 19.8 mmol). The solution was allowed to slowly warm up to ambient temperature overnight. An aqueous saturated $NaHCO_3$ solution (50 mL) was then added and the reaction mixture was stirred for another 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were concentrated to give crude **47.**

Compound **47** was dissolved in acetone/water (120 mL, 9:1). Then, the monohydrate of *N*-methylmorpholine *N*-oxide (3.16 g, 27.0 mmol) and osmium tetroxide (2.5 wt% solution in 2-methyl-2-propanol, 11.3 mL, 0.900 mmol) were added and the mixture was stirred at ambient temperature overnight. It was then diluted with an aqueous saturated sodium sulfite solution (50 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were concentrated, and the residue was diluted with THF (35 mL) and water (35 mL) followed by addition of sodium periodate (5.77 g, 27.0 mmol). After stirring at ambient temperature for one hour, the solution was diluted with an aqueous solution of saturated sodium sulfite (50 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes/EtOAc, 95:5) to afford **48** (3.58 g, 77%) as a yellow oil. $[\alpha]^{23}_D$ 27.43 (c = 3.5,

$CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 2713, 1726, 1463; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (d, J = 2.2 Hz, 1H), 4.28 (dq, J = 5.2, 6.2 Hz, 1H), 2.48 (ddq, J = 2.2, 5.2, 7.1 Hz, 1H), 1.22 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 7.1 Hz, 3H), 1.03-1.08 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 69.4, 54.0, 21.3, 18.1, 12.6, 9.7; HRMS (ESI, *m/z*) calcd for $C_{14}H_{31}O_2Si$ 259.20878, found 259.20850.

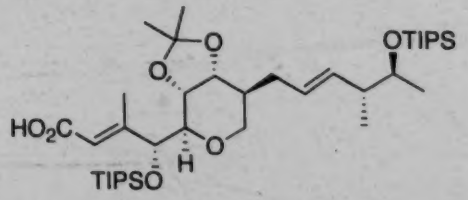
(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-O-Isopropylidene-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-triisopropylsilyloxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoyl-oxy-ethane (49)



A solution of **44** (4.29 g, 6.19 mmol) in THF (90 mL) at –78 °C was treated dropwise with potassium bis (trimethylsilyl) amide (14.8 mL, 0.500 M solution in toluene, 7.40 mmol) under argon. The resulting yellow solution was stirred at –78 °C for 0.5 h, after which time a solution of **48** (1.91 g, 7.40 mmol) in THF (40 mL) was slowly introduced *via* syringe. The reaction mixture was stirred at –78 °C for 1.5 h and then allowed to warm to ambient temperature overnight. The cloudy white reaction mixture was quenched with water (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes/ether, 95:5) to afford **49** (3.41 g, 76%) as yellow oil. $[\alpha]^{23}_D$ –0.98 (c = 5.6, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 2943, 1720, 1652; ^1H NMR (500

MHz, $CDCl_3$) δ 5.86 (s, 1H), 5.32-5.46 (m, 2H), 4.13-4.29 (m, 3H), 4.09 (dd, *J* = 2.5, 5.0 Hz, 1H), 3.88-3.93 (m, 2H), 3.58-3.62 (m, 2H), 3.28 (dd, *J* = 5.0, 9.0 Hz, 1H), 2.26-2.32 (m, 1H), 2.12-2.22 (m, 5H), 1.90-1.96 (m, 1H), 1.48 (s, 3H), 1.30 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.05-1.13 (m, 45H), 1.00 (d, *J* = 7.0 Hz , 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 158.6, 135.7, 127.2, 117.0, 108.4, 80.5, 79.1, 75.5, 71.7, 70.4, 66.0, 59.6, 44.1, 36.8, 33.7, 28.3, 26.4, 19.2, 18.2, 18.1, 18.0, 17.9, 15.9, 14.3, 14.1, 12.6, 12.5; HRMS (ESI, *m/z*) calcd for $C_{40}H_{76}O_7Si_2Na$747.50218, found 747.50259.

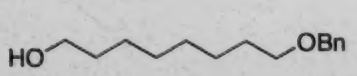
(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-O-Isopropylidene-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-triisopropylsilyloxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoic acid (50)



To a solution of **49** (3.40 g, 4.47 mmol) in ether/THF (121 mL, 10:1) was added $KOSiMe_3$ (2.55 g, 17.9 mmol). The resulting mixture was stirred at 45 °C for 20 h. The cloudy reaction mixture was then quenched with an aqueous saturated $KHSO_4$ solution (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford the title compound (3.15 g, 96%) as yellow oil. $[\alpha]^{23}_D$ 0.85 (c = 13.9, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 2943, 2891, 1694, 1647; ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (s, 1H), 5.32-5.46 (m, 2H), 4.21 (d, *J* = 4.7 Hz, 1H), 4.12 (dd, *J* = 2.3, 5.0 Hz, 1H), 3.88-3.93 (m, 2H), 3.60-3.63 (m, 2H), 3.29 (dd, *J* =

5.0, 9.0 Hz, 1H), 2.26-2.32 (m, 1H), 2.12-2.22 (m, 5H), 1.91-1.97 (m, 1H), 1.48 (s, 3H), 1.31 (s, 3H), 1.05-1.13 (m, 45H), 1.00 (d, J = 6.9 Hz , 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 161.3, 135.7, 127.2, 116.7, 108.5, 80.4, 79.3, 75.6, 71.8, 70.4, 65.9, 44.1, 36.8, 33.7, 28.2, 26.3, 19.2, 18.2, 18.1, 18.0, 17.9, 16.2, 14.1, 12.6, 12.6; HRMS (ESI, *m/z*) calcd for $C_{38}H_{72}O_7Si_2Na$ 719.47088, found 719.47079.

8-Benzyloxy-1-octanol (51)

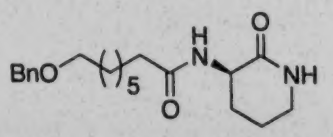


To a stirred suspension of NaH (60% oil dispersion, 1.61 g, 40.3 mmol) in DMF (30 mL) was added dropwise a solution of 1,8-octanol (5.85 g, 40.0 mmol) in THF/DMF (60 mL, 2:1) at 0 °C under argon. The mixture was stirred at 0 °C for 2 h, and benzyl bromide (5.00 mL, 42.0 mmol) was added dropwise to the mixture at 0 °C. After being stirred at ambient temperature overnight, the cloudy white reaction mixture was quenched with water (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes/EtOAc 5:1 to 1:1) to afford **51** (5.29 g, 56%) as a colorless oil. IR ($CHCl_3$, cast, cm^{-1}) 3372, 3030, 1495, 1204; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.37 (m, 5H), 4.50 (s, 2H), 3.82 (t, J = 6.6 Hz, 2H), 3.42 (t, J = 6.6 Hz, 2H), 1.42-1.62 (m, 4H), 1.20-1.40 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 128.3, 127.6, 127.5, 72.9, 70.5, 63.1, 32.8, 29.7, 29.4, 29.3, 26.1, 25.7; HRMS (EI, *m/z*) calcd for $C_{15}H_{24}O_2$ 236.17763, found: 236.17743.

8-Benzyloxy-1-octanoic acid (52)

To the solution of 8-benzyloxy-1-octanol (**51**) (4.13 g, 17.5 mmol) in wet DMF (40 mL) was added PDC (23.0 g, 61.1 mmol) at 0 °C. The resulting mixture was allowed to warm up to ambient temperature and was stirred overnight. The reaetion mixture was then poured into a separatory funnel containing water (320 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes/EtOAc 3:1) to afford **52** (3.41 g, 78%). IR ($CHCl_3$, cast, cm^{-1}) 3030, 2933, 1708, 1496; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.37 (m, 5H), 4.50 (s, 2H), 3.42 (t, J = 6.4 Hz, 2H), 2.38 (t, J = 7.4 Hz, 2H), 1.59-1.68 (m, 4H), 1.30-1.40 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 138.7, 128.3, 127.6, 127.5, 72.9, 70.4, 33.8, 29.7, 29.0, 28.9, 26.0, 24.6; HRMS (EI, *m/z*) calcd for $C_{15}H_{22}O_3$ 250.15689, found 250.15624.

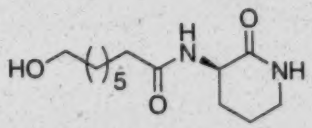
(*R*)-3-(8-Benzyloxy-1-octanoylamino)-2-piperidinone (54)



To the solution of 8-benzyloxy-1-octanoic acid (**52**) (0.750 g, 3.00 mmol) in THF (4 mL) was added 1,1'-carbonyldiimidazole (5.32 g, 3.30 mmol). The mixture was stirred at ambient temperature for 2 h and (*R*)-3-amino-2-piperidinone (**53**) (0.342 g, 3.00 mmol) was added to the solution. After stirring at ambient temperature overnight, the reaction mixture was quenched with water (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography

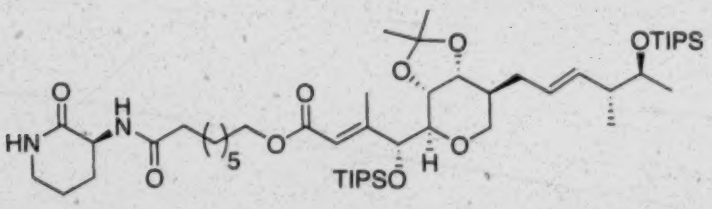
(EtOAc/MeOH 95:5) to afford product **54** (0.75 g, 72%) as a white solid. Mp 70-72 °C; $[\alpha]^{23}_D$ +50.8 (c = 0.5, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3306,, 2930, 1685, 1627, 1496; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.37 (m, 5H), 6.42 (br s, 1H), 6.02 (br s, 1H), 4.50 (s, 2H), 4.26 (ddd, *J* = 5.7, 5.7, 11.4 Hz, 1H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.32-3.37 (m, 2H), 2.55-2.65 (m, 1H), 2.21 (t, *J* = 7.3 Hz, 2H), 1.86-1.96 (m, 2H), 1.30-1.66 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 171.8, 138.7, 128.3, 127.6, 127.4, 72.8, 70.4, 50.5, 41.7, 36.6, 29.7, 29.1, 27.2, 26.0, 25.5, 21.0; HRMS (EI, *m/z*) calcd for $C_{20}H_{30}O_3N_2$ 346.22565, found 346.22493.

(*R*)-3-(8-Hydroxy-1-octanoylamino)-2-piperidinone (55)



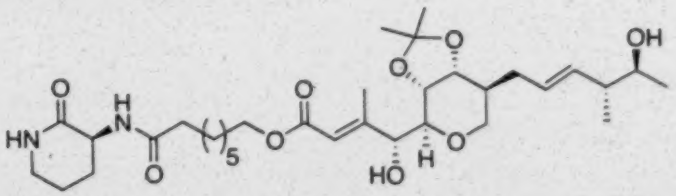
To a solution of benzyl ether **54** (0.180 g, 0.520 mmol) in EtOAc (8 mL) was added 10% Pd/C (50.0 mg). The resulting suspension was charged with a hydrogen balloon. After stirring overnight at ambient temperature, the mixture was filtered through a short-plug of Celite and washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* afford the title product **55** (128 mg, 96%) as a white foam. $[\alpha]^{23}_D$ 68.53 (c = 1.5, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3276, 2857, 1651; ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (brs, 1H), 6.12 (brs, 1H), 4.26 (ddd, *J* = 5.7, 5.7, 11.4 Hz, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.32-3.37 (m, 2H), 2.55-2.65 (m, 1H), 2.21 (t, *J* = 7.0 Hz, 2H), 1.86-1.96 (m, 3H), 1.30-1.66 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 171.9, 62.7, 50.4, 41.6, 36.4, 32.6, 29.0, 28.9, 27.2, 25.5, 25.4, 21.0; HRMS (EI, *m/z*) calcd for $C_{13}H_{24}O_3N_2$ 256.17868, found 256.17823.

(3*R*)-[(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-O-Isopropylidene-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-triisopropylsilyloxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoyl-oxy-octanoylamino]-2-piperidinone (56)



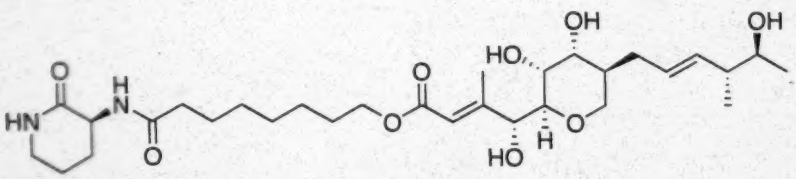
A mixture of the above acid **50** (0.328 g, 0.470 mmol), (*R*)-3-(8-Hydroxy-1-octanoylamino)-2-piperidinone (**55**) (0.110 g, 0.430 mmol), DMAP (26.0 mg, 0.220 mmol) and 1,3-diisopropylcarbodiimide (59.0 mg, 0.470 mmol) in CH_2Cl_2 (6 mL) was stirred for 48 h at ambient temperature. A drop of acetic acid followed by CH_2Cl_2 (20 mL) were then added and the precipitated urea was filtered off. The residue obtained after removal solvent was purified by flash column chromatography (EtOAc/MeOH 9:1) to afford **56** (380 mg, 95%) as yellow oil. $[\alpha]^{23}_D$ 15.57 (c = 3.9, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3291, 2892, 1660; ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (d, *J* = 4.8 Hz, 1H), 6.02 (br s, 1H), 5.88 (s, 1H), 5.30-5.46 (m, 2H), 4.26 (ddd, *J* = 5.8, 5.8, 11.6 Hz, 1H), 4.18 (d, *J* = 4.5 Hz, 1H), 4.04-4.12 (m, 3H), 3.85-3.93 (m, 2H), 3.58-3.62 (m, 2H), 3.32-3.38 (m, 2H), 3.27 (dd, *J* = 4.7, 9.0 Hz, 1H), 2.52-2.62 (m, 1H), 2.10-2.32 (m, 8H), 1.86-1.98 (m, 3H), 1.48-1.68 (m, 5H), 1.46 (s, 3H), 1.26-1.36 (m, 9H), 0.96-1.16 (m, 48H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 171.8, 166.8, 158.4, 135.6, 127.2, 117.1, 108.4, 80.4, 79.1, 75.5, 71.7, 70.4, 66.0, 63.7, 50.6, 44.1, 41.7, 36.8, 36.5, 33.7, 29.1, 29.0, 28.7, 28.3, 27.2, 26.4, 25.8, 25.5, 21.0, 19.2, 18.2, 18.2, 18.0, 18.0, 16.0, 14.1, 12.6, 12.6; HRMS (ESI, *m/z*) calcd for $C_{51}H_{95}O_9N_2Si_2$ 935.65707, found 935.65724.

(3*R*)-[(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-O-Isopropylidene-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5- hydroxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-hydroxy-but-2*E*-enoyl-oxy-octanoylamino]-2-piperidinone (57)



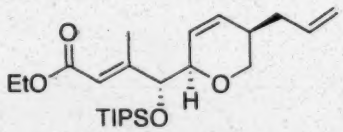
To the solution of **56** (0.220 g, 0.235 mmol) in THF (3 mL) was added TBAF (1.50 mL. 1.00 M solution in THF, 1.50 mmol). The reaction was stirred at ambient temperature for 11 h and quenched with an saturated aqueous solution of NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (20 mL) brine (20 mL), dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (EtOAc/MeOH 9:1) to afford the title compound **57** (0.119 g, 81%) as a white foam. $[\alpha]^{23}_D$ 22.10 (c = 1.5, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3305, 2932, 1712, 1653; ^1H NMR (500 MHz, $CDCl_3$) δ 6.42 (d, *J* = 4.8 Hz, 1H), 6.02 (s, 1H), 5.86 (brs, 1H), 5.42-5.55 (m, 2H), 4.26 (ddd, *J* = 5.6, 5.6, 11.2 Hz, 1H), 4.16-4.20 (m, 2H), 4.07-4.12 (m, 3H), 3.73 (dd, *J* = 3.1, 11.5 Hz, 1H), 3.66 (dd, *J* = 1.5, 11.5 Hz, 1H), 3.58 (dq, *J* = 7.2, 7.2 Hz, 1H), 3.40-3.43 (m, 1H), 3.31-3.36 (m, 2H), 2.58-2.62 (m, 1H), 2.00-2.28 (m, 9H), 1.90-1.96 (m, 3H), 1.60-1.65 (m, 4H), 1.46 (s, 3H), 1.31-1.40 (m, 9H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 171.9, 166.7, 157.3, 134.9, 129.0, 116.3, 108.8, 77.6, 75.6, 75.2, 71.1, 70.3, 66.5, 63.9, 50.6, 44.6, 41.7, 36.6, 36.5, 34.0, 28.9, 28.8, 28.5,28.3, 27.2, 26.3, 25.8, 25.4, 20.9, 20.5, 16.6, 15.8; HRMS (ESI, *m/z*) calcd for $C_{33}H_{54}N_2O_9Na$ 645.37215, found 645.37229.

(3*R*)-[(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-hydroxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-hydroxy-but-2*E*-enoyl-oxy-octanoylamino-2-piperidinone (2)



A solution of **57** (32.0 mg, 0.056 mmol) in 80% aqueous AcOH (0.65 mL) was allowed to stir at ambient temperature for 20 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/MeOH 9:1) to afford the title compound **2** (27.0 mg, 90%) as a yellow oil. $[\alpha]^{23}_{D}$ –2.25° (c = 0.004, MeOH), {lit. $[\alpha]^{23}_{D}$ –1.8 (c = 0.003, MeOH)};[4a] IR ($CHCl_3$, cast, cm^{-1}) 3325, 2928, 2858, 1716, 1652, 1456; ^1H NMR (500 MHz, $CDCl_3$) 6.68 (brs 1H), 6.42 (brs, 1H), 6.06 (brs, 1H), 5.50 (dt, *J* = 15.5, 6.1 Hz, 1H), 5.44 (dd, *J* = 15.5, 7.3 Hz), 4.35 (br s, 1H), 4.23-4.33 (m, 1H), 4.06-4.18 (m, 2H), 3.98 (brs, 1H), 3.81-3.91 (m, 2H), 3.71 (brd, *J* = 8.7 Hz, 1H), 3.50-3.60 (m, 2H), 3.29-3.39 (m, 2H), 3.12 (brs, 4H), 2.46-2.52 (m, 1H), 2.05-2.26 (m, 8H), 1.82-1.96 (m, 3H), 1.60-1.66 (m, 5H), 1.30-1.42 (m, 6H), 1.16 (d, *J* = 6.0 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 172.0, 166.9, 158.5, 134.5, 129.2, 115.8, 76.1, 73.8, 71.2, 70.5, 65.2, 64.7, 64.0, 50.4, 44.6, 41.7, 41.4, 36.4, 32.4, 28.8, 28.7, 28.3, 27.3, 26.0, 25.4, 21.0, 20.5, 16.7, 15.9; ^{13}C NMR (125 MHz, CD_3OD) δ 176.0, 173.0, 168.7, 161.2, 135.7, 129.9, 116.2, 77.6, 74.4, 72.1, 71.8, 66.0, 65.7, 64.8, 50.8, 45.3, 44.0, 42.8, 37.0, 33.4, 30.1, 30.0, 29.8, 28.9, 27.0, 26.7, 22.3, 20.3, 16.7, 16.2; HRMS (ESI, *m/z*) calcd for $C_{30}H_{50}N_2O_9Na$ 605.34085, found 605.34051.

(4*R*)-((2*S*,5*R*)-5-Allyl-5,6-dihydro-2*H*-pyran-2-yl)-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoyl-oxy-ethane (58)

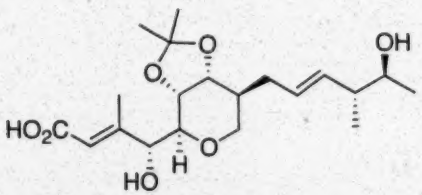


To a solution of oxalyl chloride (0.310 g, 2.40 mmol) in CH_2Cl_2 (1 mL) was added DMSO (0.380 g in 0.600 mL CH_2Cl_2, 4.80 mmol) at -78 °C. After being stirred for 0.5 h, compound **41** in 1 mL CH_2Cl_2 was added to the reaction mixture. The stirring was continued for 1 h. Triethylamine (0.730 g, 7.20 mmol) was then added. After 10 min at -78 °C, the resulted cloudy solution was allowed to warm up to ambient temperature. The solution was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (25 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated to afford crude aldehyde.

To a suspension of methyltriphenylphosphonium bromide (0.640 g, 1.80 mmol) in THF (8 mL) was added NaHMDS (1.50 mL, 1.00 M solution in THF, 1.50 mmol). The reaction mixture was stirred for 0.5 h at -78 °C, then 0.5 h at 0 °C. The crude aldehyde from previous step in THF (2 mL) was then added to the reaction mixture. The yellow solution was allowed warm slowly to ambient temperature and stirred overnight. The reaction mixture was quenched with a saturated solution of aqueous NH_4Cl (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes/ether, 95:5) to afford **58** (0.410 g, 81%) as a yellow oil. $[\alpha]^{23}_D$ 37.46 (c = 1.2, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 2944, 1718, 1652; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83-5.89 (m, 2H), 5.68-5.82 (m, 2H), 4.98-5.06 (m, 2H), 4.33 (d, *J*

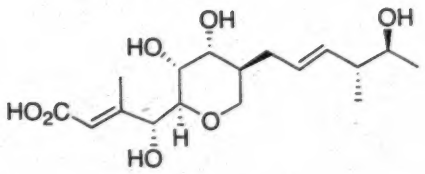
= 5.5 Hz, 1H), 4.21-4.26 (m, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.62-3.72 (m, 2H), 2.16 (s, 3H), 2.06-2.12 (m, 2H), 1.98-2.03 (m, 1H), 1.48 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.02-1.11 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 158.0, 136.4, 130.1, 125.8, 117.5, 116.4, 78.7, 77.5, 66.7, 59.6, 37.7, 34.4, 18.0, 16.6, 14.3, 12.3; HRMS (ESI, *m/z*) calcd for $C_{24}H_{42}O_4SiNa$ 445.27446, found 445.27440.

(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-O-Isopropylidene-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-hydroxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-hydroxy-but-2*E*-enoic acid (61)



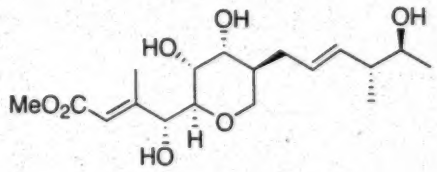
Prepared as described for compound **57**. **61** was obtained as a yellow oil. $[\alpha]^{23}_D$ – 7.8 (c = 0.3, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3420, 1690, 1646; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.41-5.57 (m, 2H), 4.12-4.22 (m, 3H), 3.75 (dd, *J* = 3.1, 11.5 Hz, 1H), 3.66 (dd, *J* = 1.6, 11.5 Hz, 1H), 3.55-3.63 (m, 1H), 3.41 (dd, *J* = 2.3, 8.4 Hz, 1H), 2.00-2.32 (m, 7H), 1.48 (s, 3H), 1.38 (s, 3H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 159.7, 134.9, 128.9, 115.9, 108.8, 77.7, 75.6, 75.3, 71.2, 70.2, 66.5, 44.4, 36.5, 34.0, 28.3, 26.3, 20.3, 16.6, 16.0; HRMS (ESI, *m/z*) calcd for $C_{20}H_{33}O_7$ 385.22208, found 385.22213.

(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-hydroxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-hydroxy-but-2*E*-enoic acid (62a)



Prepared as described for compound **2**. **62a** was obtained as a colorless oil. $[\alpha]^{23}_{D}$ 1.33 (c = 1.4, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3385, 1693, 1655; ^1H NMR (500 MHz, CD_3OD) δ 6.02 (s, 1H), 5.39-5.51 (m, 2H), 4.36 (s, 1H), 3.92 (dd, *J* = 3.0, 3.0 Hz, 1H), 3.82 (dd, *J* = 3.0, 9.5 Hz, 1H), 3.76 (dd, *J* = 2.6, 11.3 Hz, 1H), 3.68 (dd, *J* = 1.6, 9.5 Hz, 1H), 3.60 (dq, *J* = 5.7, 5.7 Hz, 1H), 3.53 (d, *J* = 11.3 Hz, 1H), 3.41 (dd, *J* = 2.3, 8.4 Hz, 1H), 2.23-2.29 (m, 1H), 2.08-2.18 (m, 5H), 1.70-1.76 (m, 1H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 170.5, 160.9, 135.7, 129.9, 116.6, 77.6, 74.4, 72.2, 71.9, 66.0, 65.8, 45.4, 43.9, 33.5, 20.3, 26.7, 16.2; HRMS (ESI, *m/z*) calcd for $C_{17}H_{28}O_7Na$ 367.17273, found 367.17258.

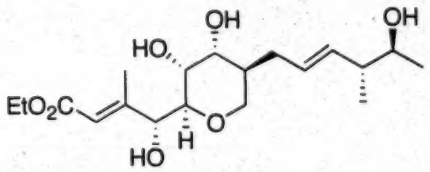
(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-hydroxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-hydroxy-but-2*E*-enoyl-oxy-methane (62b)



To a solution of compound **61** (0.130 g; 0.340 mmol) in DMF (1.5 mL) at ambient temperature was added $KOSiMe_3$ (0.047 g, 0.370 mmol). After 10 min at ambient temperature, MeI (0.145 g, 1.00 mmol) was added. The mixture was then stirred overnight at ambient temperature. After which the mixture was diluted with EtOAc (20 mL) and washed with H_2O (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, concentrated to afford crude ester which was used without purification.

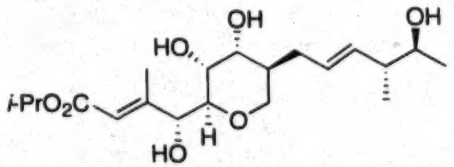
The ketal protecting group in the crude ester was removed as described in the synthesis of **2**. $[\alpha]^{23}_{D}$ 9.02 (c = 0.57, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3420, 1705, 1655; ^1H NMR (500 MHz, $CDCl_3$) δ 6.04 (s, 1H), 5.41-5.53 (m, 2H), 4.31 (s, 1H), 3.99 (brs, 1H), 3.85-3.91 (m, 2H), 3.72 (s, 3H), 3.66 (dd, *J* = 2.0, 9.6 Hz, 1H), 3.53-3.59 (m, 2H), 3.41 (dd, *J* = 2.3, 8.4 Hz, 1H), 2.06-2.26 (m, 6H), 1.82-1.88 (m, 1H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 158.7, 134.4, 129.0, 115.3, 75.8, 73.7, 71.4, 70.4, 65.3, 64.6, 51.1, 44.5, 41.5, 32.4, 20.6, 16.8, 16.0; HRMS (ESI, *m/z*) calcd for $C_{18}H_{31}O_7$ 359.20643, found 359.20673.

(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-hydroxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-hydroxy-but-2*E*-enoyl-oxy-ethane (62c)



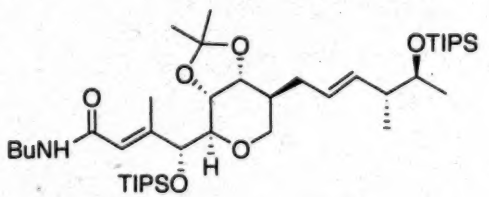
Prepared as described for compound **62c**. $[\alpha]^{23}_{D}$ 13.86 (c = 3.1, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3419, 1700, 1653; ^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.36-5.52 (m, 2H), 4.30 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.96 (brs, 1H), 3.82-3.89 (m, 2H), 3.66 (dd, *J* = 1.5, 9.5 Hz, 1H), 3.52-3.58 (m, 2H), 2.03-2.23 (m, 6H), 1.82-1.88 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 158.2, 134.5, 129.1, 115.8, 75.8, 73.8, 71.4, 70.4, 65.3, 64.6, 59.8, 44.6, 41.5, 32.4, 20.6, 16.8, 16.0, 14.3; HRMS (ESI, *m/z*) calcd for $C_{19}H_{33}O_7$ 373.22208, found 373.22238.

2-[(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-hydroxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-hydroxy-but-2*E*-enoyl-oxy]-propane (62d)



Prepared as described for compound **62d**. $[\alpha]^{23}_{D}$ 10.94 (c = 3.1, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3412, 197, 1655; ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (s, 1H), 5.38-5.53 (m, 2H), 5.04 (septet, *J* = 6.3 Hz, 1H), 4.28 (d, *J* = 8.8 Hz, 1H), 3.96 (brs, 1H), 3.82-3.88 (m, 2H), 3.67 (dd, *J* = 1.6, 9.4 Hz, 1H), 3.52-3.58 (m, 2H), 3.39 (d, *J* = 5.5 Hz, 1H), 3.12 (d, *J* = 9.4 Hz, 1H), 3.01 (s, 1H), 2.20-2.35 (m, 6H), 1.82-1.88 (m, 1H), 1.26 (d, *J* = 6.3 Hz, 6H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 157.8, 134.6, 129.1, 116.3, 75.9, 73.9, 71.4, 70.4, 67.1, 65.3, 64.7, 44.6, 41.5, 32.5, 22.0, 20.7, 16.8, 15.9; HRMS (ESI, *m/z*) calcd for $C_{20}H_{34}O_7Na$ 409.21968, found 409.21960.

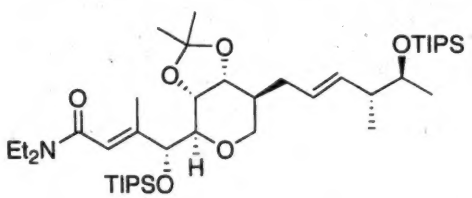
(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-O-Isopropylidene-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-triisopropylsilyloxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoic acid butylamide (63a)



To a solution of **50** (0.220 g, 0.320 mmol) in CH_2Cl_2 (1.5 mL) at ambient temperature was added sequentially PyBrop (0.180 g, 0.380 mmol) and butylamine

(0.028 g, 0.380 mmol) followed by Hunig's base (0.130 g, 1.00 mmol). After being stirred at ambient temperature overnight, the mixture was diluted with EtOAc (30 mL) and washed with H_2O (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (hexanes/EtOAc, 5:1) to afford **63a** (0.195 g, 82%) as yellow oil. $[\alpha]^{23}_D$ 3.13 (c = 0.3, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3294, 1662, 1653; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.59 (t, *J* = 5.5 Hz, 1H), 5.32-5.48 (m, 2H), 4.09-4.15 (m, 2H), 3.85-3.93 (m, 2H), 3.59-3.62 (m, 2H), 3.22-3.38 (m, 3H), 2.26-2.32 (m, 1H), 2.16-2.22 (m, 2H), 2.05 (s, 3H), 1.90-1.96 (m, 1H), 1.43-1.55 (m, 5H), 1.31-1.42 (m, 5H), 1.03-1.10 (m, 45H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 149.9, 135.7, 127.2, 120.3, 108.3, 80.2, 79.1, 75.6, 71.7, 71.0, 66.0, 44.1, 38.9, 36.8, 33.8, 31.8, 28.3, 26.4, 20.2, 19.2, 18.2, 18.2, 18.1, 18.0, 15.4, 14.1, 13.7, 12.6, 12.6; HRMS (ESI, *m/z*) calcd for $C_{42}H_{82}NO_6Si_2$ 752.56752, found 752.56731.

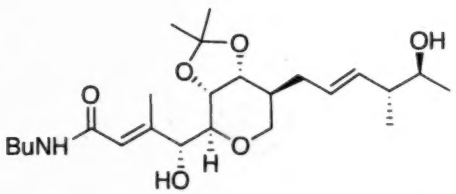
(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-O-Isopropylidene-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-triisopropylsilyloxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-triisopropylsilyloxy-but-2*E*-enoic acid diethylamide (63b)



Prepared as described for compound **63a**. $[\alpha]^{23}_D$ -9.65 (c = 0.97, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 2942, 1656, 1631; ^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.38-5.46 (m, 2H), 4.20 (d, *J* = 4.5 Hz, 1H), 4.08 (dd, *J* = 2.3, 5.0 Hz, 1H), 3.86-3.98 (m, 2H),

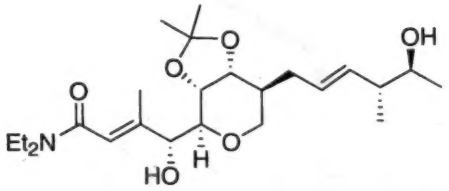
3.58-3.62 (m, 2H), 3.34-3.3.46 (m, 4H), 3.28 (dd, J = 4.3, 8.9 Hz, 1H), 2.26-2.32 (m, 1H), 2.16-2.22 (m, 2H), 1.88-2.00 (m, 4H), 1.46 (s, 3H), 1.32 (s, 3H), 1.12-1.16 (m, 51H), 1.00 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 146.7, 135.6, 127.2, 119.9, 108.3, 80.3, 78.7, 75.7, 71.7, 70.7, 65.8, 44.1, 36.9, 33.7, 28.3, 26.4, 19.2, 18.2, 18.1, 18.1, 18.1, 15.4, 14.1, 12.7, 12.6; HRMS (ESI, *m/z*) calcd for $C_{42}H_{82}NO_6Si_2$ 752.56752, found 752.56780.

(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-O-Isopropylidene-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-hydroxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-hydroxy-but-2*E*-enoic acid butylamide (64a)



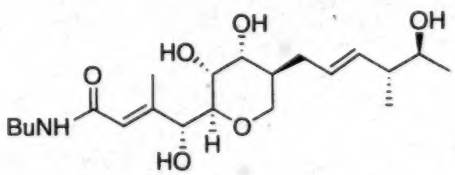
Prepared as described for compound **57**. $[\alpha]^{23}_D$ -3.86 (c = 0.84, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3320, 1669, 1635; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (s, 1H), 5.42-5.60 (m, 3H), 4.13-4.20 (m, 2H), 4.06 (s, 1H), 3.73 (dd, J = 1.7, 11.5 Hz, 1H), 3.66 (d, J = 11.5 Hz, 1H), 3.58 (t, J = 6.1 Hz, 2H), 3.38-3.43 (m, 1H), 3.26-3.32 (m, 2H), 2.02-2.26 (m, 7H), 1.46-1.53 (m, 5H), 1.32-1.40 (m, 5H), 1.16 (d, J = 6.2 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.93 (t, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 150.6, 134.9, 128.9, 119.0, 108.7, 77.5, 75.7, 74.9, 71.1, 70.4, 66.4, 44.5, 39.0, 36.5, 34.1, 31.7, 28.3, 26.3, 20.5, 20.1, 16.7, 15.3, 13.7; HRMS (ESI, *m/z*) calcd for $C_{24}H_{42}NO_6$ 440.30066, found 440.30006.

(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-O-Isopropylidene-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-hydroxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-hydroxy-but-2*E*-enoic acid diethylamide (64b)



Prepared as described for compound **53**. $[\alpha]^{23}_{D}$ -12.89 (c = 0.63, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3393, 1653, 1607; ^1H NMR (500 MHz, $CDCl_3$) δ 6.16 (s, 1H), 5.45-5.57 (m, 2H), 4.18-4.22 (m, 2H), 4.10 (s, 1H), 3.74 (dd, *J* = 3.2, 11.7 Hz, 1H), 3.66 (d, *J* = 1.4, 11.7 Hz, 1H), 3.58 (dq, *J* = 6.3, 6.3 Hz, 1H), 3.35-3.43 (m, 5H), 2.18-2.26 (m, 2H), 2.08-2.12 (m, 1H), 2.02-2.08 (m, 1H), 1.96 (s, 3H), 1.50 (s, 3H), 1.36 (s, 3H), 1.12-1.28 (m, 9H), 1.02 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 146.3, 134.6, 129.0, 119.2, 108.5, 77.6, 75.7, 74.6, 71.0, 70.5, 66.5, 44.3, 42.4, 39.4, 36.6, 34.3, 28.3, 26.3, 20.4, 16.5, 15.4, 14.3, 13.1; HRMS (ESI, *m/z*) calcd for $C_{24}H_{42}NO_6$ 440.30066, found 440.30033.

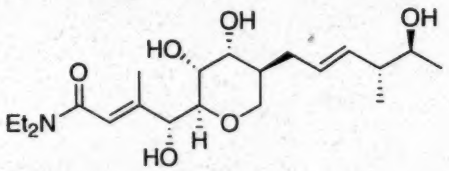
(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-hydroxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-hydroxy-but-2*E*-enoic acid butylamide (65a)



Prepared as described for compound **2**. $[\alpha]^{23}_{D}$ 14.37 (c = 0.16, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3346, 1667, 1634; ^1H NMR (500 MHz, $CDCl_3$) δ 5.98 (s, 1H), 5.95

(brs, 1H), 5.40-5.52 (m, 2H), 4.26 (s, 1H), 3.96 (s, 1H), 3.82-3.88 (m, 2H), 3.67 (d, J = 8.9 Hz, 1H), 3.52 -3.58 (m, 2H), 3.25-3.32 (m, 2H), 2.02-2.12 (m, 6H), 1.82-1.88 (m, 1H), 1.46-1.53 (m, 2H), 1.32-1.40 (m, 2H), 1.16 (d, J = 6.1 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 151.2, 134.6, 128.8, 118.7, 76.2, 73.3, 71.3, 70.7, 65.0, 64.8, 44.4, 41.5, 39.2, 32.3, 31.6, 20.7, 20.2, 16.9, 15.5, 13.8; HRMS (ESI, *m/z*) calcd for $C_{21}H_{38}NO_6$ 400.26936, found 400.26975.

(4*R*)-{(2*S*,3*R*,4*R*,5*S*)-3,4-dihydroxy-5-[(4*R*,5S)-4-methyl-5-hydroxy-hex-2-enyl]-tetrahydro-pyran-2-yl}-3-methyl-4-hydroxy-but-2*E*-enoic acid diethylamide (65b)



Prepared as described for compound **2**. $[\alpha]^{23}_D$ 25.39 (c = 0.48, $CHCl_3$); IR ($CHCl_3$, cast, cm^{-1}) 3391, 1653, 1600; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (s, 1H), 5.39-5.53 (m, 2H), 4.25 (s, 1H), 3.95 (s, 1H), 3.86 (dd, J = 2.5, 11.4 Hz, 1H), 3.83 (dd, J = 3.1, 9.6 Hz, 1H), 3.65 (dd, J = 2.8, 9.3 Hz, 1H), 3.52 -3.58 (m, 2H), 3.36-3.50 (m, 5H), 2.06-2.26 (m, 3H), 1.86-1.91 (m, 4H), 1.12-1.19 (m, 9H), 0.99 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 146.1, 134.3, 129.3, 119.0, 76.2, 73.3, 71.1, 70.6, 65.3, 64.9, 44.5, 42.8, 41.4, 39.5, 32.5, 20.4, 16.6, 15.7, 14.2, 13.0; HRMS (ESI, *m/z*) calcd for $C_{21}H_{38}NO_6$ 400.26936, found 400.26975.

5.7.3. Bioassay

Staphylococcus aureus strains were ATCC#25923 and ATCC#6538. Meuller-Hinton broth (Difco#275730) was used at 2.1% (w/v) and agar (Difco#214010) was used at 1.7%. Blank 6 mm sterile paper discs were purchased from BD. Disk diffusion tests were performed following the Clinical and Laboratory Standards Institute guidelines (formerly NCCLS; publication M2-A8). *S. aureus* was grown on trypticase soy agar. Five fresh colonies were inoculated into 4 ml trypticase soy broth and grown about five hours, standing, at 35°C. Cultures were adjusted to A_{625} of 0.1 (0.5 McFarland Standard) and streaked on Meuller-Hinton agar plates using a sterile cotton swab. All compounds were dissolved in 25% methanol in water. Disks were loaded with compounds in 15 µl of the appropriate solvents as indicated and placed on the agar plates. Plates were incubated for about 17 hours at 35°C and zones of inhibition were recorded. All plates were done in duplicate for each *S. aureus* strain.

5.6. References

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Chavez's thesis : Chavez, D. E. Ph.D. Thesis, Harvard University, **2005**, pp 75-112.

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45. The anti-microbial activity assay was carried out by Dr. Sandra Marcus at Department of Chemistry, University of Alberta.

Chapter 6

Thesis Conclusions

This thesis described research aimed at the development and application of tandem three-component Diels-Alder cycloaddition/allylboration reactions to access α-hydroxyalkyl cyclohexene derivatives and chiral α-hydroxyalkyl dihydropyran derivatives. The development of these methodologies was stimulated by a variety of biologically interesting natural products containing these kinds of structural motifs, which were previously difficult to access efficiently using existing methodologies.

During the course of our investigations on the three-component normal electron demand Diels-Alder cycloaddition/allylboration involving electronically enriched 1-boronobutadienes, we needed to find a mild method to access these diene substrates after the failure of a number of obvious methods. This method relies on the hydroboration of enynes with pinacolborane catalyzed by Schwartz's reagent. Although these electronically enriched dienes did not demonstrate the anticipated increase in reactivity with moderately activated dienophiles at low temperatures, the success of the three-component reaction with 1-borono-3-triethylsilyloxy-1,3-butadiene pinacolate provides a new stereoselective approach to polysubstituted cyclohexene intermediates with potential use in the synthesis of complex natural products. Moreover, it is noteworthy that these dienylboronates are appealing intermediates for use in Suzuki coupling reactions as well. In fact, at least two groups contacted us and showed their interests on using these dienes in Suzuki coupling.

The major part of this thesis deals with our effort on developing and applying a three-component catalytic asymmetric inverse electron demand hetero-Diels-Alder cycloaddition/allylboration sequence to access α-hydroxyalkyl dihydropyran derivatives. These efforts were motivated by the occurrence of this unit in the structure of several bioactive natural products. We envisioned that the presence of an electron-withdrawing boronate substituent on 3-boronoacrolein pinacolate would make it a very reactive heterodiene in the inverse electron demand Diels-Alder reaction with enol ethers catalyzed by Jaconsen's chiral Cr(III) catalyst. Indeed, 3-boronoacrolein pinacolate was found to be an exceptionaly reactive diene in the hetero-Diels-Alder reaction using ethyl vinyl ether as the dienophile and the cycloadduct was obtained with excellent diastero- (>98% de) and enantioselectivity (96% ee). This reaction represents the first example of a preparation of chiral allylic boronate by an catalytic asymmetric approach. Due to the high reactivity of 3-boronoacrolein pinacolate, the catalyst loading in the cycloaddition reaction can be reduced to as low as 0.3 mol%, which is very impressive when compared to loading values of 5-10 mol% previously reported for a wide range of α,β-unsaturated aldehydes. After comparing the reactivity of 3-boronoacrolein pinacolate with ethyl (*E*)-4-oxobutenoate, we realized that the exceptional reactivity of 3-boronoacrolein pinacolate could not be attributed solely to the electron-withdrawing ability of the boronate group. Based on previous studies by Singleton and co-workers on the Diels-Alder reactions of vinyl boranes, a [5+2] transition state involving a three-center two-electron system was proposed. As anticipated, the chiral cycloadduct successfully undergoes an allylboration reaction with a variety of aldehydes to provide α-hydroxyalkyl dihydropyran derivatives with very high diastero- (>98% de) and enantioselectivity (96% ee). Moreover, the

hetero-Diels-Alder cycloaddition/allylboration sequence was found to be amenable to a "one-pot" procedure. Overall, this three-component reaction represents one of the most efficient ways to access chiral α-hydroxyalkyl dihydropyrans and substituted pyrans in general.

These chiral dihydropyran derivatives can serve as starting materials to access a variety of structural motifs such as δ–lactones. We thus applied the catalytic asymmetric three-component reaction in a concise synthesis of (5*R*,6*S*)-6-acetoxy-hexadecanolide, the major component of the oviposition attractant pheromone of *Culex* mosquito (the primary vector of West Nile Virus) and its C6 epimer. The synthesis of (5*R*,6*S*)-6-acetoxy-hexadecanolide was completed in seven steps from commercially available propionaldehyde diethyl acetal in 35% overall yield. The synthesis of (5*R*,6*R*)-6-acetoxy-hexadecanolide was accomplished in six steps in an impressive overall yield of 55%.

Thiomarinols are promising leads for antimicrobial drug discovery. In response to the increasing demand for new antimicrobial agents, we developed an efficient synthetic route to a member of the potent thiomarinol family of antibiotics using a tandem hetero-Diels-Alder cycloaddition/allylboration sequence. It was demonstrated for the first time that acyclic 2-substituted enol ethers, a class of notoriously difficult substrates in the inverse electron demand hetero-Diels-Alder reaction, are viable dienophiles provided that 3-boronoacrolein pinacolate is employed as the heterodiene under the catalysis of Jacobsen's chiral Cr(III) catalyst. The high reactivity of 3-boronoacrolein pinacolate as a heterodiene successfully overcomes the low reactivity of 2-substituted enol ethers as

dienophilic partners. Moreover, the fortuitous but very useful discovery of catalyst-controlled *Z*-enol ether selectivity in the Cr(III)-catalyzed cycloaddition reaction significantly advances the existing methodology originally developed by Jacobsen and co-workers. This highly efficient synthetic route to thiomarinol, which was achieved in 14 steps in 22% overall yield from 3-boronoacrolein, greatly facilitates our efforts at generating thiomarinol analogs. To date, a number of analogues have been synthesized and two of the simplified ester analogues demonstrated better antibacterial activity than that of the natural product. Further work on the analogues of thiomarinols could lead to the discovery of new antibacterial agent that could help meet the increasing demand for treatment of bacterial infections.

Appendices

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Appendix A

X-Ray crystallography report of compound 25 (Chapter 2)

Structure report

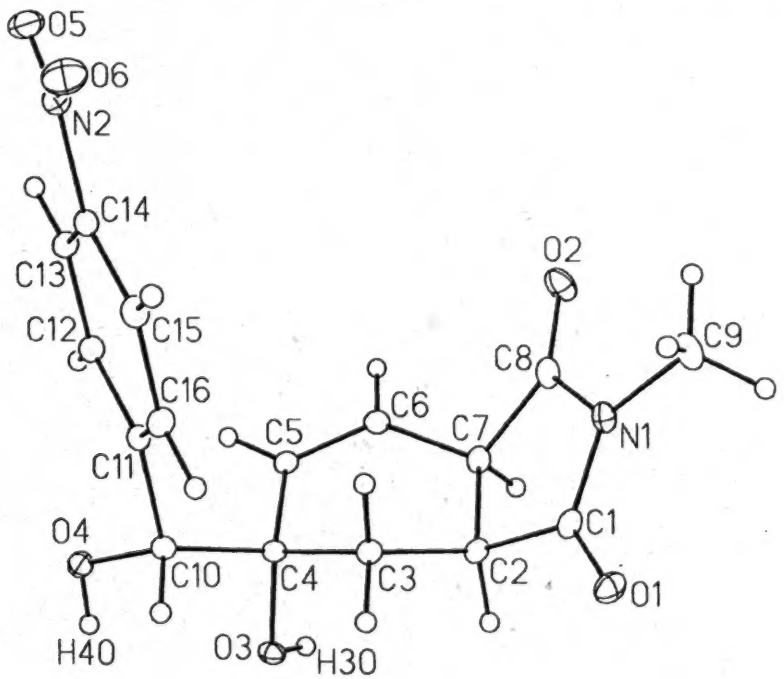
XCL Code: DGH0205

Date: 31 July 2002

Compound: 4-Hydroxy-8-methyl-4-*p*-nitrophenylhydroxymethyl-8-azabicyclo[4.3.0]non-2-ene-7,9-dione

Formula: $C_{16}H_{16}N_2O_6$

Supervisor: D. G. Hall **Crystallographer:** R. McDonald



Appendix B

X-Ray crystallography report of compound 38 (Chapter 3)

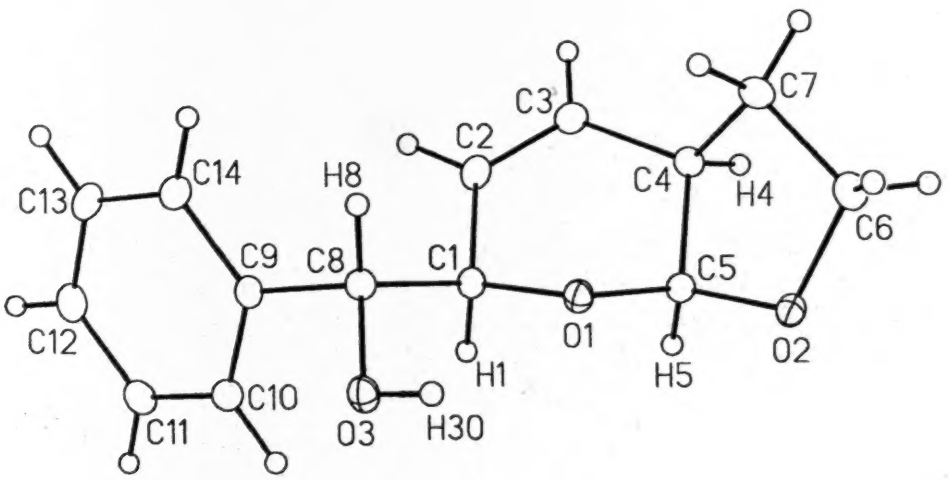
Structure report

XCL Code: DGH0501 **Date:** 8 March 2005

Compound: 6-α-Hydroxybenzyl-2,3,3a,7a-tetrahydro-6*H*-furo[2,3-*b*]pyran (*relative stereochemistry determination*)

Formula: $C_{14}H_{16}O_3$

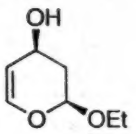
Supervisor: D. G. Hall **Crystallographer:** R. McDonald



Appendix C

Chiral HPLC analysis for compound 29 (Chapter 3)

(chiralpak AD-RH, racemate)



File C:\HPCHEM\1\DATA\XURI\G1R00000.D Sample Name: G1R

sample in methanol

Injection Date	: 6/28/02 3:15:38 PM	Seq. Line	: 1
Sample Name	: G1R	Vial	: 1
Acq. Operator	: xuri	Inj	: 1
		Inj Volume	: 1 µl
Method	: D:\TEMP\1\METHOD$\XURI\CHIRAL1.M		
Last changed	: 6/28/02 3:13:13 PM by xuri		

chiral HPLC with 50% isopropanol/H20 for 15 minutes; DAD detector, flow rate of 0.300 ml/min

DAD1 C, Sig=210,8 Ref=360,100 (XURIG1R0000C.D)

Area Percent Report

Sorted By	:	Signal
Multiplier	:	1.0000
Dilution	:	1.0000

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.822	VB	0.2516	1.81213e4	1080.97449	48.9639
2	10.611	PB	0.2929	1.88882e4	971.05341	51.0361
Totals :				3.70095e4	2052.02789	

*** End of Report ***

Gradient(LCMSD) 6/28/02 4:50:11 PM xuri Page 1 of 1

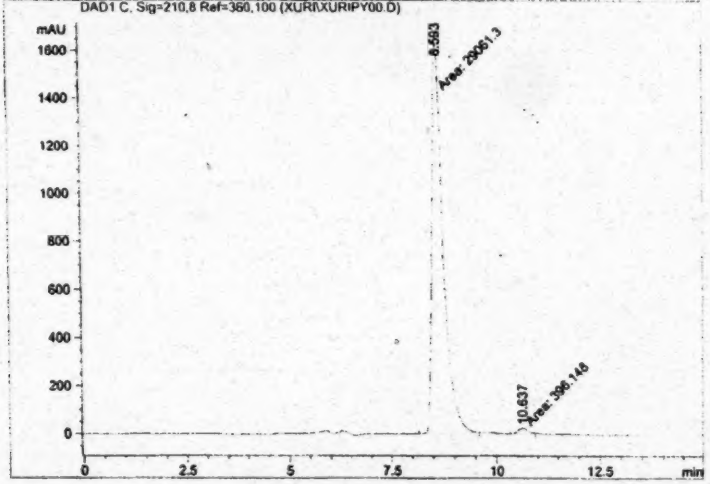
Chiral HPLC analysis for compound 29 (Chapter 3)

(chiralpak AD-RH, enantiomer)

Data File C:\HPCHEM\1\DATA\XURI\XURIPY00.D Sample Name: BaO0.25

BaO, 0.25% catalyst

```
Injection Date  : 5/10/03 12:30:13 PM
Sample Name     : BaO0.25                          Vial :   1
Acq. Operator   : xuri
                                                Inj Volume : 1 µl
Method          : D:\TEMP\1\METHODS\XURI\CHIRAL1.M
Last changed    : 5/10/03 12:27:05 PM by xuri
                  (modified after loading)
chiral HPLC with 50% isopropanol/H20 for 15 minutes; DAD detector; flow rate of 0.300 ml/min
```

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                        Area Percent Report

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/ul]   (not used in calc.)

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1   8.593 MM    0.2963 2.90613e4  1634.53772  98.6552
   2  10.637 MM    0.2813  396.14810   23.46716   1.3448

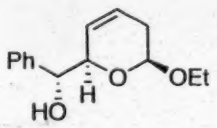
Totals :                  2.94575e4  1658.00488

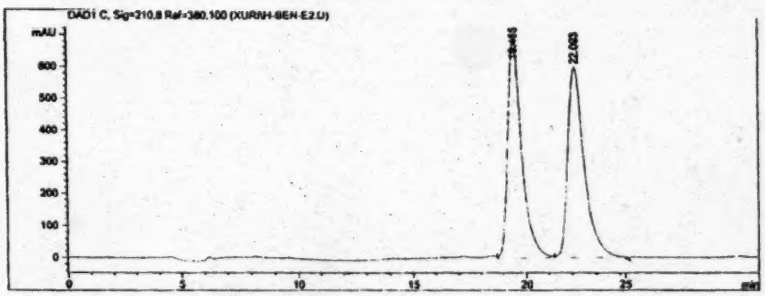
                        *** End of Report ***
```

Appendix D

Chiral HPLC analysis for compound 18a (Chapter 3)

(chiralpak AD-RH, racemate and enantiomer)



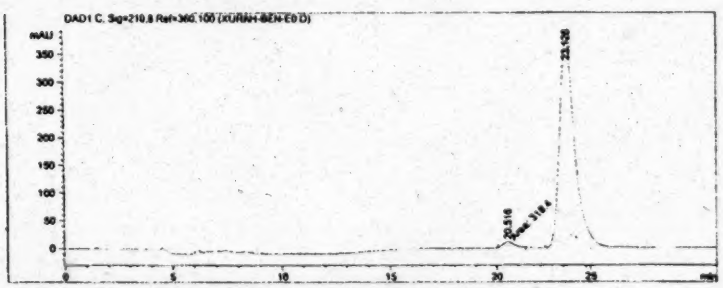


Area Percent Report

Sorted By	:	Signal	
Multiplier	:	1.0000	
Dilution	:	1.0000	
Sample Amount	:	1.00000 [ng/ul]	(not used in calc.)

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.465	VV	0.6221	2.87080e4	691.84680	50.2289
2	22.093	VB	0.7165	2.84463e4	598.54248	49.7711



Area Percent Report

Sorted By	:	Signal	
Multiplier	:	1.0000	
Dilution	:	1.0000	
Sample Amount	:	1.00000 [ng/ul]	(not used in calc.)

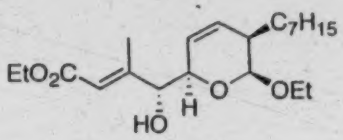
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

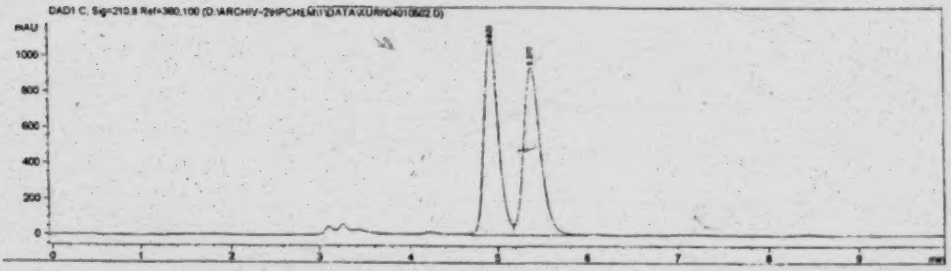
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.516	MM	0.5728	318.40030	9.26426	1.8073
2	23.128	PB	0.6975	1.72989e4	374.10635	98.1927

Appendix E

Chiral HPLC analysis for compound 18a (Chapter 5)

(chiralpak AS, racemate and enantiomer)

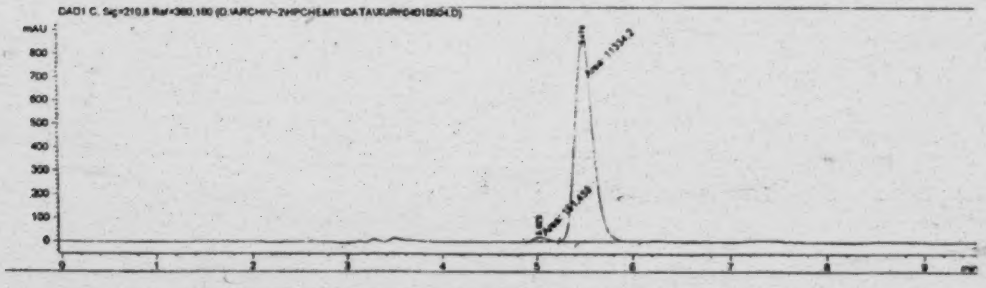




Area Percent Report

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.925	BV	0.1669	1.22535e4	1126.59265	50.1278
2	5.377	VB	0.1995	1.21910e4	938.92169	49.8722



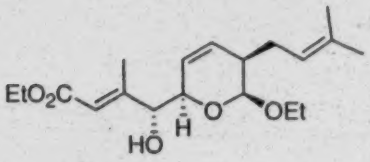
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

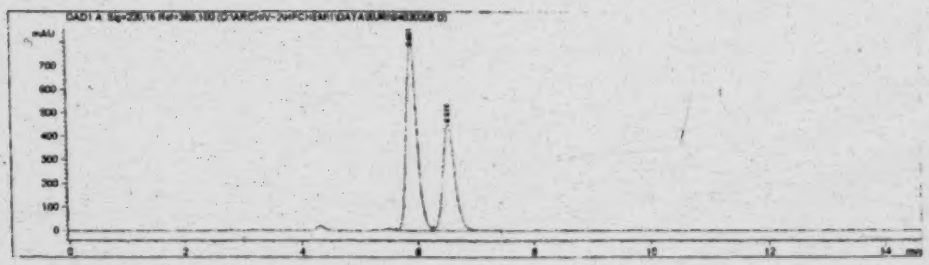
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	
1	5.023	MM	0.1788	191.45940	17.84569	1.6612	
2	5.476	MM	0.2133	1.13342e4	885.82068	98.3388	calc.)

Appendix F

Chiral HPLC analysis for compound 18d (Chapter 5)

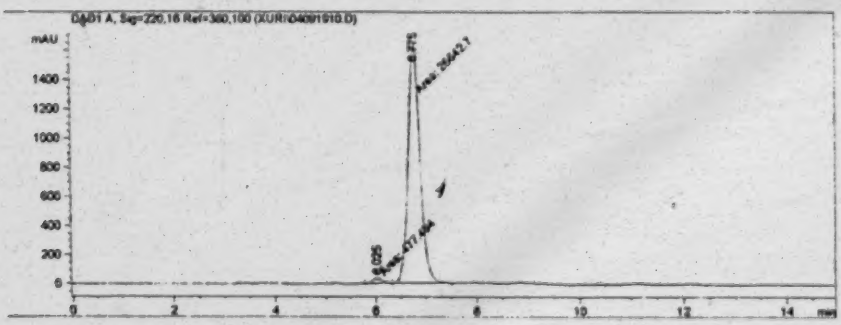
(chiralpak AS, racemate and enantiomer)





Signal 1: DAD1 A, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.891	VV	0.1909	1.01692e4	819.02581	60.6071
2	6.533	VB	0.2252	6609.70850	430.32080	39.3929



Area Percent Report

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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

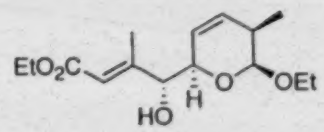
Signal 1: DAD1 A, Sig=220,16 Ref=360,100

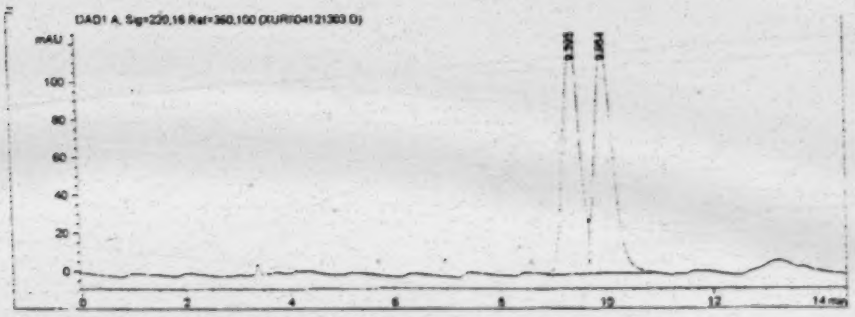
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.025	MF	0.2280	477.49368	34.90574	1.7607
2	6.775	FM	0.2722	2.66427e4	1631.39563	98.2393

Appendix G

Chiral HPLC analysis for compound 36a (Chapter 5)

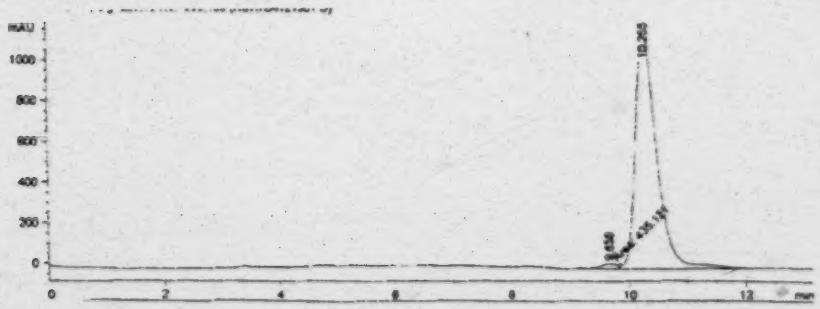
(chiralpak AS, racemate and enantiomer)





Signal 1: DAD1 A, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.395	BV	0.3476	2678.33398	122.25690	48.5933
2	9.964	VB	0.3586	2833.40283	120.39508	51.4067

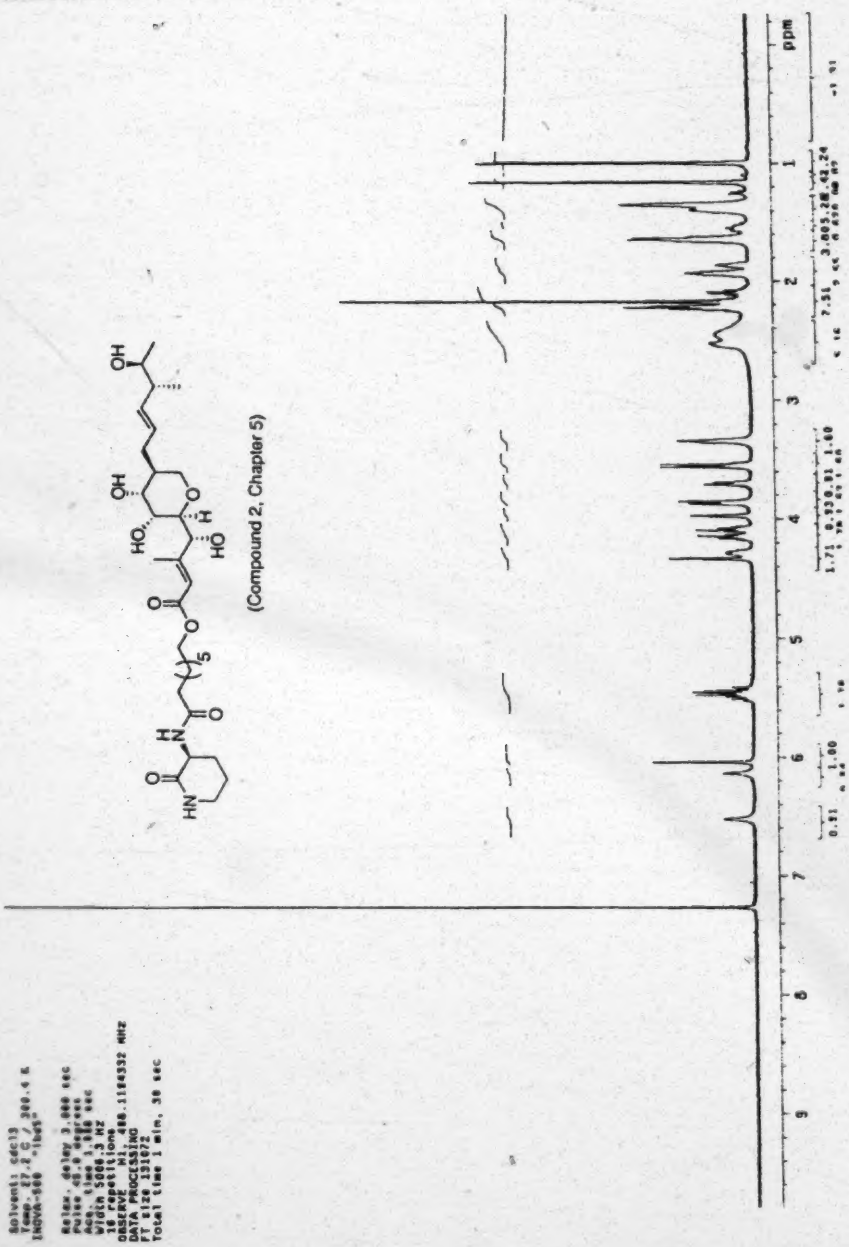


Signal 1: DAD1 A, Sig=220,16 Ref=360,100

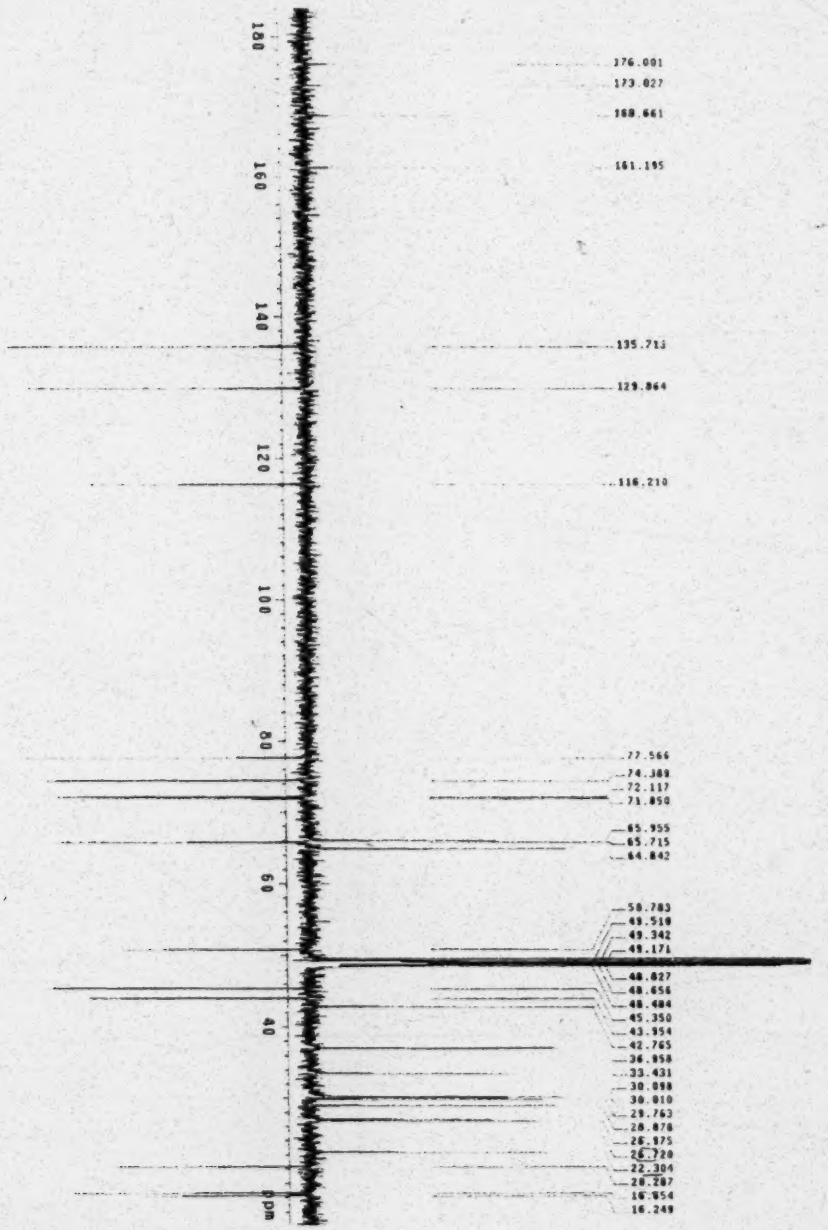
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.658	MM	0.3099	435.12122	23.39742	1.4594
2	10.255	VV	0.3863	2.93807e4	1157.02124	98.5406

Appendix H

^{1}H-NMR and APT spectra of natural product 2 (Chapter 5)



Kurt Gao, XG-S-196
125 MHz APT in CD3OD (ref. to CD3OD @ 49.0 ppm)



Pulse Sequence: apt